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Office of Chemical Safety and
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Draft Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP)

CASRN: 872-50-4

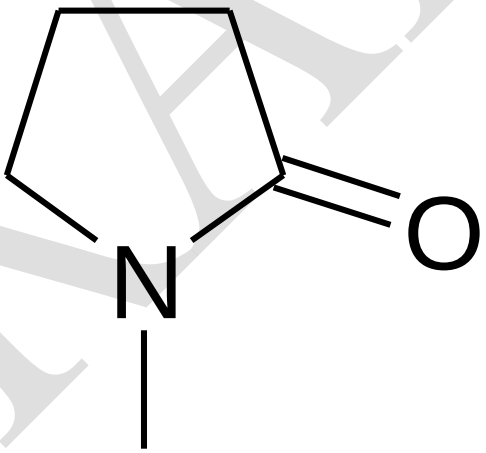

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDIX TABLES

LIST OF APPENDIX FIGURES

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Docket
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ABBREVIATIONS

°C	Degrees Celsius
atm	Atmosphere(s)
ATSDR	Agency for Toxic Substances and Disease Registry
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
CAA	Clean Air Act
CASRN	Chemical Abstracts Service Registry Number
CBI	Confidential Business Information
CCL	Contaminant Candidate List
CDR	Chemical Data Reporting
CEM	Consumer Exposure Model
CFR	Code of Federal Regulations
cm^3	Cubic Centimeter(s)
COC	Concentration of Concern
DTSC	Department of Toxic Substances Control
EC	European Commission
EC_{50}	Effective Concentration with 50% immobilized test organisms
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-to-Know Act
ESD	Emission Scenario Document
EU	European Union
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug and Cosmetic Act
GBL	Gamma-Butyrolactone
GS	Generic Scenarios
HESIS	Hazard Evaluation System and Information Service
HHE	Health Hazard Evaluation
HPV	High Production Volume
Hr	Hour
IMAP	Inventory Multi-Tiered Assessment and Prioritisation
IRIS	Integrated Risk Information System
kg	Kilogram(s)
L	Liter(s)
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
lb	Pound(s)
LC_{50}	Lethal Concentration to 50% of test organisms
LOEC	Lowest Observed Effect Concentration
Log K_{oc}	Logarithmic Soil Organic Carbon:Water Partition Coefficient
Log K_{ow}	Logarithmic Octanol:Water Partition Coefficient
m^3	Cubic Meter(s)
MADL	Maximum Allowable Dose Level
mg	Milligram(s)
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration

ONU	Occupational Non-User
µg	Microgram(s)
MMA	Monomethylamine
mmHg	Millimeter(s) of Mercury
mPa·s	Millipascal(s)-Second
MITI	Ministry of International Trade and Industry
SDS	Safety Data Sheet
MSW	Municipal Solid Waste
NAICS	North American Industry Classification System
NESHAP	National Emission Standards for Hazardous Air Pollutants
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NIOSH	National Institute for Occupational Safety and Health
NMP	N-Methylpyrrolidone
NWQMC	National Water Quality Monitoring Council
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organisation for Economic Cooperation and Development
OEHHA	Office of Environmental Health Hazard Assessment
OEL	Occupational Exposure Limits
OPPT	Office of Pollution Prevention and Toxics
OSHA	Occupational Safety and Health Administration
PBZ	Personal Breathing Zone
PDE	Permissible Daily Exposure
PDM	Probabilistic Dilution Model
PECO	Populations, Exposures, Comparisons, Outcomes
PEL	Permissible Exposure Limit
PF	Protection Factor
POD	Point of Departure
POTW	Publicly Owned Treatment Works
PPE	Personal Protective Equipment
ppm	Part(s) per Million
PSD	Particle Size Distribution
RCRA	Resource Conservation and Recovery Act
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SDWA	Safe Drinking Water Act
SIDS	Screening Information Data Set
STORET	STOrage and RETrieval
SVHC	Substance of Very High Concern
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	Time-Weighted Average
USGS	United States Geological Survey
VOC	Volatile Organic Compound
WEEL	Workplace Environmental Exposure Level
Yr	Years

EXECUTIVE SUMMARY

This draft risk evaluation for N-methylpyrrolidone (NMP) was performed in accordance with the Frank R. Lautenberg Chemical Safety for the 21st Century Act and is being disseminated for public comment and peer review. The Frank R. Lautenberg Chemical Safety for the 21st Century Act amended the Toxic Substances Control Act (TSCA), the Nation's primary chemicals management law, in June 2016. As per EPA's final rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726), EPA is taking comment on this draft, and will also obtain peer review on this draft risk evaluation for NMP. All conclusions, findings, and determinations in this document are preliminary and subject to comment. The final risk evaluation may change in response to public comments received on the draft risk evaluation and/or in response to peer review, which itself may be informed by the public comments. The preliminary conclusions, findings, and determinations in this draft risk evaluation are for the purpose of identifying whether the chemical substance presents unreasonable risk or no unreasonable risk under the conditions of use, in accordance with TSCA section 6, and are not intended to represent any findings under TSCA section 7.

TSCA § 26(h) and (i) require EPA to use scientific information, technical procedures, measures, methods, protocols, methodologies and models consistent with the best available science and to base its decisions on the weight of the scientific evidence. To meet these TSCA § 26 science standards, EPA used the TSCA systematic review process described in the Application of Systematic Review in TSCA Risk Evaluations document (U.S. EPA, 2018a). The data collection, evaluation, and integration stages of the systematic review process are used to develop the exposure, fate, and hazard assessments for risk evaluations.

N-Methylpyrrolidone (CASRN 872-50-4), also called n-methyl-2-pyrrolidone, or 1-methyl-2-pyrrolidone, is a water-miscible, organic solvent that is often used as a substitute for halogenated solvents. NMP exhibits a unique set of physical-chemical properties that have proven useful in a range of industrial, commercial and consumer applications. NMP has low volatility and high affinity for aromatic hydrocarbons, which makes it effective for solvent extraction in petrochemical processing and pharmaceutical manufacturing. NMP is also valued for its high polarity and low surface tension which are considered optimal for solvent cleaning and surface treatment of metals, textiles, resins, and plastics. NMP is subject to federal and state regulations and reporting requirements. NMP has been a reportable chemical to Toxics Release Inventory (TRI) substance under Section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA) since January 1, 1995.

NMP is widely used in the chemical manufacturing, petrochemical processing and electronics industries. There is also growing demand for NMP use in semiconductor fabrication and lithium ion battery manufacturing (FMI, 2015). In the commercial sector, NMP is primarily used for producing and removing paints, coatings and adhesives. Other applications include, but are not limited to, use in solvents, reagents, sealers, inks and grouts. EPA evaluated the following categories of conditions of use for NMP: manufacturing; processing; distribution in commerce, industrial, commercial and consumer uses and disposal. The total aggregate production volume for NMP decreased slightly from 164 to 160 million pounds between 2012 and 2015.

Approach

EPA used reasonably available information (defined in 40 CFR 702.33 as "information that EPA possesses, or can reasonably generate, obtain, and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation) in a "fit-for-purpose" approach, to develop a risk evaluation that relies on the best available science and is based on the weight of the scientific evidence. EPA used previous analyses as a starting point for identifying key and supporting studies to inform the exposure, fate, and hazard assessments. EPA also evaluated other studies that were published since these reviews. EPA reviewed the information and evaluated the quality of the methods and reporting of results of the individual studies using the evaluation strategies described in Application of Systematic Review in TSCA Risk Evaluations (U.S. EPA, 2018a).

In the problem formulation document, EPA identified the NMP conditions of use and presented three conceptual models and an analysis plan for the current draft risk evaluation. In this draft risk evaluation, EPA evaluated risks to aquatic species from environmental releases to surface water associated with the manufacturing, processing, distribution, use and disposal of NMP. EPA also evaluated the risks posed to workers and consumers, as well as occupational non-users (i.e., workers who do not directly handle NMP but perform work in an area where it is used) and consumer bystanders (i.e., non-users who are incidentally exposed to NMP as a result of the use of consumer products containing NMP).

Exposures

EPA evaluated acute and chronic exposures for aquatic species as a screening level risk assessment for ambient surface water exposures associated with NMP environmental releases from the manufacturing, processing, distribution, use and disposal. EPA used environmental release data from EPA's Toxics Release Inventory (TRI) to derive conservative estimates of NMP surface water concentrations (acute and chronic) near facilities reporting the highest NMP water releases.

NMP may occur in various environmental media including sediment, soil, water and air. As part of the NMP Problem Formulation (U.S. EPA, 2018c), EPA completed a preliminary analysis of environmental exposures for aquatic terrestrial species to NMP in these environmental media. No additional information has been received or otherwise identified by EPA that would alter the conclusions presented in the NMP Problem Formulation (U.S. EPA, 2018c). EPA concluded that no further analysis of environmental release pathways for environmental receptors is necessary based on a qualitative assessment of the physical chemistry and fate properties of NMP and the levels of NMP exposure that may be expected for organisms that inhabit these environmental compartments.

EPA evaluated acute and chronic human exposures by the dermal and inhalation routes, including direct contact with NMP-containing liquids and indirect exposure from vapor-through-skin uptake. For each occupational use scenario, EPA considered moderate and high-end exposure parameters and the impact of different combinations of personal protective equipment (PPE) on exposure. Empirical data were preferred for exposure estimation when available. In the absence of measured data, EPA used models to estimate exposure to the human receptors of interest. The models' underlying input parameters and assumptions were based on reasonably available information regarding NMP physical and chemical properties, NMP weight fraction in the product, and the activity patterns associated with use. Exposure to individuals located near those using NMP-containing products (i.e., nearby non-users,) were also estimated based on inhalation and vapor-through-skin uptake.

EPA used two different approaches to quantify acute exposures to consumers. The first approach incorporated assumptions based on the duration of use; whereas the second approach incorporated assumptions regarding the specific type of project involved (e.g., paint stripping a table, chest of drawers, or bathtub).

Hazards

EPA identified acute and chronic Concentrations of Concern (COCs) for aquatic organisms based on the available acute and chronic hazard data for NMP. These acute and chronic COCs are compared to the estimated surface water concentrations of NMP from the exposure assessment.

Reported outcomes in laboratory animal studies range from irritation to decreased body weight and adverse systemic effects (e.g., liver, kidney, spleen, thymus, testes, brain). EPA reviewed the reasonably available information on hazard potential and selected reproductive and developmental toxicity endpoints in rodents (i.e., fetal mortality and decreased fertility) as the critical effects for dose-response analysis and risk estimation. EPA identified fetal mortality as the critical endpoint for acute exposures and reduced fertility as the critical endpoint for chronic exposures.

Other outcomes, including adverse systemic effects, may occur at higher exposure concentrations. The risk determinations in the current document are based on adverse developmental effects observed in a potentially exposed or susceptible subpopulation (e.g., pregnant women and women of child bearing age who may become pregnant) which are expected to be protective of other outcomes and other potentially exposed or susceptible subpopulations.

Human Populations Considered in This Risk Evaluation

EPA assumed those who use NMP-containing products would be adults of either sex (>16 years old), including pregnant women, and evaluated risks to individuals who do not use NMP but may be indirectly exposed due to their proximity to the user who is directly handling NMP or the product containing NMP.

The risk evaluation is based on potential effects on fertility as well as developmental toxicity. The lifestages of greatest concern for developmental effects are pregnant women and women of childbearing age who may become pregnant. Lifestages of concern for effects on reproductive health and fertility include men and women of reproductive age as well as children and adolescents. The risk evaluation is intended to be protective of other potentially exposed or susceptible subpopulations, including people with pre-existing conditions and people with genetic variations that make them more susceptible. Exposures that do not present risks based on sensitive reproductive and developmental endpoints are not expected to present risks for other potential health effects of NMP because other health effects occur at higher levels of exposure.

Risk Characterization

This draft risk evaluation characterizes the environmental and human health risks from NMP under the conditions of use, including manufacture, processing, distribution, use, and disposal.

Environmental Risks: For environmental risk, EPA utilized a risk quotient (RQ) to compare the estimated acute and chronic NMP exposure concentrations in surface water to respective acute and chronic COCs to characterize the risk to aquatic organisms. A screening level risk analysis for NMP in

surface water and aquatic receptors resulted in RQs for the acute and chronic risk of 0.0022 and 0.85, respectively (Table 4-2). An RQ that does not exceed 1 indicates that the exposure concentrations of NMP are less than the concentrations expected to produce an adverse effect. Because the RQ values do not exceed 1, and because EPA used a conservative screening level approach, these values indicate that the risks of NMP to the aquatic organisms are unlikely. NMP is not likely to accumulate in sediment based on its physical chemical properties and is not expected to adsorb to sediment due to its water solubility and low partitioning to organic matter. Because NMP toxicity to sediment-dwelling organisms is expected to be comparable to that of aquatic organisms, minimal risks are anticipated for sediment-dwelling organisms. NMP exhibits low volatility and readily biodegrades under aerobic conditions; therefore, the concentrations in ambient air are unlikely to reach levels that would present risks for terrestrial organisms. Details of these estimates are in section 4.1.2.

Human Health Risks: For human health risks to workers and consumers, EPA identified non-cancer human health risks. Based on the exposure scenarios evaluated, risks may be anticipated for individuals who are not directly exposed to liquid NMP (e.g., occupational non-user, consumer bystander) as a result of indirect exposure via inhalation and vapor through skin exposures. Generally, risks identified for workers are linked to chronic exposures, whereas risks for consumers are linked to acute exposures. Although glove use may be effective in reducing NMP exposure, some glove types do not provide adequate protection. Further discussion and examples of appropriate glove use are included in Appendix E.

Strengths, Limitations and Uncertainties in the Risk Characterization

The exposure estimates EPA used to evaluate human health risks were based on a large amount of monitoring data and were supported by modeling data for many conditions of use. PBPK models allowed EPA to evaluate risks from aggregate exposures from simultaneous dermal and inhalation exposures. Robust evidence of a continuum of adverse reproductive and developmental effects support the hazard endpoints EPA used as the basis for evaluating risks from acute and chronic exposures. In addition, PBPK modeling reduces uncertainties around the relevance of animal data for human health. Uncertainties around the representativeness of exposure monitoring data, activity pattern information, PPE use and efficacy, and incomplete information on some hazard endpoints and factors that may contribute to increased exposure and susceptibility to NMP contribute to the overall uncertainties of the risk estimates. Overall, EPA has medium to high confidence in the risk estimates presented in this risk characterization.

Potentially Exposed and Susceptible Subpopulations (PESS)

TSCA § 6(b)(4) requires that EPA conduct a risk evaluation of PESS. In developing the risk evaluation, EPA analyzed the reasonably available information to ascertain whether some human receptor groups may have greater exposure or greater susceptibility than the general population to the hazard posed by a chemical. For consideration of the most highly exposed groups, EPA assessed NMP exposures to PESS of interest: males, pregnant women, and women of childbearing age who may become pregnant.

Aggregate and Sentinel Exposures

EPA evaluated aggregate risks from dermal and inhalation routes of exposure for each COU. Peer-reviewed PBPK modeling allowed EPA to integrate aggregate exposures across routes by translating exposure concentrations into internal doses (human blood concentrations). While this assessment evaluated specific COUs based on exposure estimates that incorporate multiple routes of exposure, it did

not consider the potential for aggregate exposures from multiple conditions of use. EPA considered sentinel exposure in the form of high-end estimates for consumer and occupational exposure scenarios which incorporate dermal and inhalation exposure, as these routes are expected to present the highest exposure potential.

Risk Determination

In each risk evaluation under TSCA section 6(b), EPA determines whether a chemical substance presents an unreasonable risk of injury to health or the environment, under the conditions of use. These determinations do not consider costs or other non-risk factors. In making these determinations, EPA considers relevant risk-related factors, including, but not limited to: the effects of the chemical substance on health and human exposure to such substance under the conditions of use (including cancer and non-cancer risks); the effects of the chemical substance on the environment and environmental exposure under the conditions of use; the population exposed (including any potentially exposed or susceptible subpopulations (PESS)); the severity of hazard (including the nature of the hazard, the irreversibility of the hazard); and uncertainties. EPA also takes into consideration the Agency's confidence in the data used in the risk estimate. This includes an evaluation of the strengths, limitations and uncertainties associated with the information used to inform the risk estimate and the risk characterization. The rationale for the risk determination is discussed in section 5.

Environmental Unreasonable Risks: For all conditions of use, EPA did not identify any scenarios indicating unreasonable risk for aquatic, sediment-dwelling, or terrestrial organisms from exposures to NMP. NMP readily degrades under aerobic conditions and is not expected to persist in the environment. Because the RQ values do not exceed 1, and because EPA used a conservative screening level approach, these values indicate that the risks of NMP to the aquatic organisms are unlikely. As a result, EPA does not find unreasonable risk to the environment for any of the conditions of use for NMP (see section 4.1.2).

Unreasonable Risk to the General Population: EPA is not including general population exposures in the risk evaluation for NMP. As explained in the Problem Formulation for the Risk Evaluation for NMP, general population exposures were determined to be outside the scope of the risk evaluation. EPA has determined that the existing regulatory programs and associated analytical processes adequately assess and effectively manage the risks of NMP that may be present in various media pathways (e.g. air, water, land) for the general population. For these cases, EPA believes that the TSCA risk evaluation should not focus on those exposure pathways, but rather on exposure pathways associated with TSCA conditions of use that are not subject to those regulatory processes, because the latter pathways are likely to represent the greatest areas of concern to EPA.

Unreasonable Risk to Workers: EPA evaluated workers' acute and chronic inhalation and dermal exposures (including uptake of vapor through skin) for non-cancer risks and determined whether any risks indicated are unreasonable risk. The drivers for EPA's determination of unreasonable risk for workers are reproductive effects from chronic inhalation and dermal exposures; generally, risks identified for workers are linked to chronic exposures. The determinations reflect the severity of the effects associated with occupational exposures to NMP and incorporate consideration of expected personal protective equipment (PPE) (frequently estimated to be gloves with a protection factor of 5, 10, or 20). For workers, EPA determined that the conditions of use that presented unreasonable risks included processing of NMP into formulations or mixtures, and many industrial or commercial uses as a

solvent or degreaser. A full description of EPA's determination for each condition of use is in section 5.2.

Unreasonable Risk to Occupational Non-Users (ONUs): EPA's exposure assessment includes estimates of NMP exposures to occupational non-users (ONUs). ONUs are located in the general vicinity near workers but are further from emissions sources. Unlike workers, ONUs do not have direct dermal contact with liquids. The estimates assume ONUs are not wearing respirators. While the difference between ONU exposures and workers directly handling the chemical generally cannot be quantified, EPA assumes that, in most cases, ONU inhalation exposures are expected to be lower than inhalation exposures for workers directly handling the chemical substance. To account for those instances where monitoring data or modeling did not distinguish between worker and ONU inhalation exposure estimates, EPA considered the central tendency risk estimate when determining ONU risk. For several conditions of use, there were risks for ONUs for high-end chronic exposures. However, risk estimates for ONUs for the central tendency scenarios did not indicate risk. EPA determined that the conditions of use assessed did not present an unreasonable risk for ONUs.

Unreasonable Risk to Consumers: EPA evaluated consumer acute inhalation, dermal, and vapor through skin exposures for non-cancer risks and determined whether the risks indicated are unreasonable. Risks for consumers were evaluated using acute exposure scenarios. The driver for EPA's determination of unreasonable risk is developmental adverse effects from acute inhalation and dermal exposure. These adverse effects include fetal mortality. EPA determined that several consumer conditions of use present unreasonable risk of injury to health. A full description of EPA's determination for each condition of use is in section 5.2.

Unreasonable Risk to Bystanders (from consumer uses): EPA's exposure assessment includes estimates of NMP exposures to bystanders (i.e. those located in the house during consumer product use) who do not have direct contact with NMP-containing consumer products. EPA did not find unreasonable risk to bystanders for the conditions of use assessed.

Summary of Risk Determinations:
EPA has determined that the following conditions of use of NMP do not present an unreasonable risk of injury to health. The details of these determinations are in table 5-1 in section 5.2.

Conditions of Use that Do Not Present an Unreasonable Risk
• Domestic manufacture • Import (including repackaging and loading/unloading) • Processing as a reactant or intermediate in several manufacturing processes, including plastic material and resin manufacturing and in pharmaceutical and medicine manufacturing • Processing as a reactant or intermediate, other • Processing for incorporation into articles in other sectors, including in plastic product manufacturing • Repackaging for wholesale and retail trade • Processing - Recycling • Distribution in commerce

Conditions of Use that Do Not Present an Unreasonable Risk
• Industrial and commercial use in ink, toner, and colorant products, including printer ink and inks in writing equipment • Industrial and commercial use in processing aids, specific to petroleum production in petrochemical manufacturing, and other uses in oil and gas drilling and pharmaceutical and medicine manufacturing • Industrial and commercial use in other uses in soldering materials • Industrial and commercial use, Other Uses, Fertilizer and Other agricultural chemical manufacturing – processing aids and solvents • Industrial and commercial use in other uses, wood preservatives • Consumer use in paints and coatings, adhesive removers • Consumer use in paints and coatings, lacquers, stains, varnishes, primers and floor finishes • Consumer use in paint additives and coating additives not described by other codes, paints and arts and crafts paints • Consumer use in adhesives and sealants single component glues and adhesives, including lubricant adhesives and two-component glues and adhesives including some resins • Consumer use in other uses in automotive care products • Consumer use in other uses lubricant and lubricant additives, including hydrophilic coatings • Disposal including industrial pre-treatment, industrial wastewater treatment publicly owned treatment works (POTW), underground injection, landfill (municipal, hazardous or other land disposal), emissions to air, incinerators (municipal and hazardous waste).

EPA determined that the following conditions of use of NMP present an unreasonable risk of injury to health to workers or to consumers. The details of these determinations are discussed in table 5-1 in section 5.2.

Processing Uses that Present an Unreasonable Risk
• Incorporation into a formulation, mixture or reaction product in several industrial sectors • Incorporation into articles as lubricants and lubricant additives in machinery manufacturing • Incorporation into articles as paint additives and coating additives not described by other codes in transportation equipment manufacturing • Incorporation into articles as a solvent (which becomes part of product formulation or mixture), including in textiles, apparel and leather manufacturing

Industrial and Commercial Uses that Present an Unreasonable Risk
• For paint and coating removers and in adhesive removers • For paint and coatings (lacquers, stains, varnishes, primers and floor finishes, and powder coatings, surface preparation), in paint additives and coating additives not described by other codes in several manufacturing sectors, and in adhesives and sealants, several types • As a solvent (for cleaning or degreasing) use in electrical equipment, appliance and component manufacturing and for other uses in manufacturing lithium ion batteries

Industrial and Commercial Uses that Present an Unreasonable Risk
• As other uses in anti-freeze and de-icing products, automotive care products and lubricants and greases • As other uses in metal products not covered elsewhere, and lubricant and lubricant additives including hydrophilic coatings • As other uses in laboratory chemicals • As other uses, cleaning and furniture care products, including wood cleaners and gasket removers

267

Consumer Uses that Present an Unreasonable Risk
• For paints and coatings, paint and coating removers • As other uses, cleaning and furniture care products, including wood cleaners and gasket removers.

268

1 INTRODUCTION

This document presents the draft risk evaluation for NMP under the Frank R. Lautenberg Chemical Safety for the 21st Century Act. The Frank R. Lautenberg Chemical Safety for the 21st Century Act amended the Toxic Substances Control Act, the Nation's primary chemicals management law, in June 2016.

The Agency published the Scope of the Risk Evaluation for NMP (U.S. EPA, 2017d) in June 2017, and the problem formulation in June, 2018 (U.S. EPA, 2018c), which represented the analytical phase of risk evaluation whereby "the purpose for the assessment is articulated, the problem is defined, and a plan for analyzing and characterizing risk is determined," as described in Section 2.2 of the *Framework for Human Health Risk Assessment to Inform Decision Making*. EPA received comments on the published problem formulation for NMP and has considered the comments specific to NMP, as well as more general comments regarding EPA's chemical risk evaluation approach for developing the draft risk evaluations for the first 10 TSCA Workplan chemicals.

During problem formulation, EPA identified the NMP conditions of use and presented the associated conceptual models and an analysis plan. In this risk evaluation, EPA evaluated risks to workers from inhalation and dermal exposures by comparing the exposure estimates for acute and chronic scenarios to the related human health hazards. While NMP is present in various environmental media such as groundwater, surface water, and air, EPA determined during problem formulation that no further analysis of the environmental release pathways associated with ecological exposures via ambient water, sediments, and land-applied biosolids was needed based on a qualitative assessment of the physical-chemical properties and fate of NMP in the environment and a quantitative comparison of the hazards and exposures identified for aquatic organisms. Risk determinations were not made as part of problem formulation; therefore, the results from these analyses are used to inform the risk determination section of this draft risk evaluation.

EPA used reasonably available information consistent with the best available science for physical-chemical and fate properties, potential exposures, and relevant hazards according to the systematic review process. For the human exposure pathways, EPA evaluated inhalation exposures to vapors and mists for workers and occupational non-users, and dermal exposures via skin contact with liquids and vapor through skin uptake for workers and consumers. EPA characterized risks to ecological receptors from exposures via surface water, sediment, and land-applied biosolids in the risk characterization section of this draft risk evaluation based on the analyses presented in the problem formulation.

This document is structured such that the Introduction (Section 1) presents the basic physical-chemical properties of NMP, and background information on its regulatory history, conditions of use and conceptual models, with emphasis on any changes since the publication of the problem formulation. This section also includes a discussion of the systematic review process utilized in this draft risk evaluation. Exposures (Section 2) provides a discussion and analysis of the exposures, both human and environmental, that can be expected based on the conditions of use identified for NMP. Hazards (Section 3), discusses the environmental and human health hazards of NMP. The Risk Characterization (Section 4), integrates the reasonably available information on human health and environmental hazards and exposures, as required by TSCA (15 U.S.C 2605(b)(4)(F)). This section also includes a discussion of the uncertainties that underly the assessment and how they impact the risk evaluation. As required

under TSCA 15 U.S.C. 2605(b)(4), a determination of whether the risk posed by this chemical substance is unreasonable is presented in the Risk Determination (Section 5).

As per EPA's final rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726) (hereinafter "Risk Evaluation Rule"), this draft risk evaluation is subject to both public comment and peer review, which are distinct but related processes. EPA is providing 60 days for public comment, which will inform the EPA Science Advisory Committee on Chemicals (SACC) peer review process. EPA seeks public comment on all aspects of this draft risk evaluation, including all conclusions, findings, and determinations. This is also an opportunity for EPA to receive additional information that might be relevant to the science underlying the draft risk evaluation and the outcome of the systematic review approach used for NMP. This review satisfies TSCA [15 U.S.C 2605(b)(4)(H)], which requires EPA to provide public notice and an opportunity for comment on a draft risk evaluation prior to publishing a final risk evaluation.

Peer review will be conducted in accordance with EPA's regulatory procedures for chemical risk evaluations, including using the *EPA Peer Review Handbook* and other methods consistent with section 26 of TSCA (*See* 40 CFR § 702.45). As explained in the Risk Evaluation Rule, the purpose of the peer review is for the independent review of the science underlying the risk evaluation. Peer review will therefore address aspects of the underlying science as outlined in the charge to the peer review panel such as hazard assessment, assessment of dose-response, exposure assessment, and risk characterization. Peer-review supports scientific rigor and enhances transparency in the risk evaluation process.

As explained in the Risk Evaluation Rule, it is important for peer reviewers to consider how the underlying risk evaluation analyses fit together to produce an integrated risk characterization, which will form the basis of an unreasonable risk determination. EPA believes peer reviewers will be most effective in this role if they receive the benefit of public comments on draft risk evaluations prior to peer review. For this reason, EPA is providing the opportunity for public comment before peer review on this draft risk evaluation. The final risk evaluation may change in response to public comments received on the draft risk evaluation and/or in response to peer review, which itself may be informed by public comments. EPA will respond to public and peer review comments received on the draft risk evaluation when it issues the final risk evaluation.

EPA solicited input on the first 10 chemicals, including NMP, as it developed use dossiers, scope documents, and problem formulations. At each step, EPA received information and comments specific to individual chemicals and of a more general nature relating to various aspects of the risk evaluation process, technical issues, and the regulatory and statutory requirements. EPA has considered comments and information received at each step in the process and factored in the information and comments as the Agency deemed appropriate and relevant including comments on the published problem formulation of NMP. Thus, in addition to any new comments on the draft risk evaluation, the public should re-submit or clearly identify at this point any previously filed comments, modified as appropriate, that are relevant to this risk evaluation and that the submitter believes have not been addressed. EPA does not intend to further respond to comments submitted prior to the publication of this draft risk evaluation unless they are clearly identified in comments on this draft risk evaluation.

1.1 Physical and Chemical Properties

Physical-chemical properties influence the environmental behavior and the toxic properties of a chemical, thereby informing the potential conditions of use, exposure pathways, routes and hazards that EPA intends to consider. During problem formulation, EPA considered the measured or estimated physical-chemical properties set forth in Table 1-1. Based on EPA's review of the available literature, the vapor pressure previously reported for NMP was updated (0.345 mmHg) to conform with EPA's data quality criteria. This value is considered more reliable than the original value (0.19 mmHg) which was taken from a secondary source.

NMP is a high boiling, polar aprotic solvent with low viscosity and low volatility. It is miscible with water and most organic solvents and exhibits low flammability and no explosivity. It is not readily oxidizable; variations in temperature and humidity can produce a range of saturation concentrations in ambient air (U.S. EPA, 2019a, 2017d).

Table 1-1. Physical-Chemical Properties of NMP

Property	Value [a]	Reference
Molecular formula	C_5H_9ON	
Molecular weight	99.1 g/mole	O'Neil et al. (2006)
Physical form	Colorless liquid	O'Neil et al. (2006)
Melting point	-25°C	Ashford (1994)
Boiling point	202°C	O'Neil et al. (2006)
Density	1.03 at 25°C	O'Neil et al. (2006)
Vapor pressure	0.345 mmHg at 25°C	Daubert and Danner (1989)
Vapor density	3.4 (air = 1)	NFPA (1997)
Water solubility	1,000 g/L at 25°C (miscible)	O'Neil et al. (2006)
Octanol:water partition coefficient (log K_{ow})	-0.38 at 25°C	Sasaki et al. (1988)
Henry's Law constant	3.2×10^{-9} atm m^3/mole	Kim et al. (2000)
Flash point	95°C (open cup)	Riddick et al. (1986)
Auto flammability	Not available	
Viscosity	1.65 mPa·s at 25°C	O'Neil et al. (2006)
Refractive index	Not applicable	
Dielectric constant	Not applicable	

[a] Measured unless otherwise noted.

1.2 Uses and Production Volume

1.2.1 Data and Information Sources

The summary of use and production volume information presented below is based on research conducted for the *Problem Formulation Document for N-Methylpyrrolidone (NMP)* (U.S. EPA, 2018c) and any additional information obtained since the publication of that document. The previous research was based on reasonably available information, including the *Use and Market Profile for NMP*, (EPA-HQ-OPPT-2016-0743); public meetings and meetings with companies, industry groups, chemical users and other stakeholders to aid in identifying and verifying the conditions of use included in this risk evaluation.

NMP is an effective solvent that is widely used in the manufacture and production of electronics, petroleum products, pharmaceuticals, polymers and other specialty chemicals. It has numerous industrial, commercial, and consumer applications. Some of the major areas of use identified for NMP are listed below (Harreus et al., 2011; Ash and Ash, 2009):

1. Petrochemical processing: acetylene recovery from cracked gas, extraction of aromatics and butadiene, gas purification (removal of CO_2 and H_2S), lube oil extraction
2. Engineering plastics: reaction medium for production of high-temperature polymers such as polyether sulfones, polyamideimides and polyaramids
3. Coatings: solvent for acrylic and epoxy resins, polyurethane paints, waterborne paints or finishes, printing inks, synthesis/diluent of wire enamels, coalescing agent
4. Specialty chemicals: solvent and/or co-solvent for liquid formulations
5. Electronics: cleaning agent for silicon wafers, photoresist stripper, auxiliary in printed circuit board technology
6. Industrial and domestic cleaning: component in paint strippers and degreasers

In addition to the uses in industrial, commercial, and consumer settings, NMP is used in ways considered as mission critical to federal agencies.

The Chemical Data Reporting (CDR) Rule under TSCA (40 CFR Part 711) requires that U.S. manufacturers and importers provide EPA with information on chemicals they manufacture (including imports). For the 2016 CDR cycle, data collected for each chemical include the company name, volume of each chemical manufactured/imported, the number of workers employed at each site, and information on whether the chemical is used in the commercial, industrial, and/or consumer sector. Only those companies that manufactured or imported at least 25,000 pounds of NMP per site were required to report under the CDR rule during the 2015 calendar year (U.S. EPA, 2017c). The 2016 CDR reporting data for NMP are provided in Table 1-2.

Table 1-2. Production Volume of NMP in CDR Reporting Period (2012 to 2015) [a]

Reporting Year	2012	2013	2014	2015
Total Aggregate Production Volume (lbs)	164,311,844	168,187,596	171,095,221	160,818,058

[a] The CDR data for the 2016 reporting period is available via ChemView (https://chemview.epa.gov/chemview) (U.S. EPA, 2017c). Because of an ongoing CBI substantiation process required by amended TSCA, the CDR data available in the risk evaluation document is more specific than currently in ChemView.

NMP is widely used in the chemical manufacturing, petrochemical processing and electronics industries (FMI, 2015). In the commercial sector, it is primarily used for producing and removing paints, coatings and adhesives. Other commercial applications include, but are not limited to, use in solvents, reagents, sealers, inks and grouts. There is also growing demand for NMP use in semiconductor fabrication and lithium ion battery manufacturing. Data reported for the 2016 CDR period (U.S. EPA, 2017c) indicate over 160 million pounds of NMP were manufactured (including imports) in the United States in 2015 (U.S. EPA, 2017c).

NMP is used in paint removers, and as a solvent/reagent for the electronics and pharmaceutical industries. It is also used as a solvent for hydrocarbon recovery in the petrochemical processing industry, and for the desulfurization of natural gas (Global Newswire, 2016; FMI, 2015). While paint removers represent a large product category for NMP, growth in this sector is uncertain as a result of the potential risks identified in the previous risk assessment published by EPA (U.S. EPA, 2015).

NMP is a key cleaning component for the manufacture of semiconductors used in electronics, and for the manufacture of printed circuit boards. As the consumer demand for electronics rises, especially in the Asia Pacific region, the global demand for NMP is expected to grow. Similar increases in NMP use may occur in other regions, albeit to a lesser degree (Grand View Research, 2016). The U.S. market revenue for NMP is also expected to increase over the next ten years despite variations in the oil and gas industry. NMP is primarily used in downstream processes, which makes it more resilient to market volatility in this sector (Grand View Research, 2016).

1.2.2 Toxics Release Inventory Data

Under the Emergency Planning and Community Right-to-Know Act (EPCRA) Section 313, NMP is a TRI-reportable substance effective January 1, 1995. During problem formulation, EPA further analyzed the TRI data and examined the definitions of elements in the TRI data to determine the level of confidence that a release would result from specific types of land disposal (e.g., RCRA Subtitle C hazardous landfill and Class I underground Injection wells) and incineration. EPA also examined how NMP is treated at industrial facilities.

Table 1-3 provides production-related waste management data for NMP reported by industrial facilities to the TRI program from reporting years 2015 to 2017.[1] In reporting year 2017, 380 facilities reported a

[1] Reporting year 2017 is the most recent TRI data available. Data presented in Table 1-3 and Table 1-4 were queried using TRI Explorer and uses the 2017 National Analysis data set (released to the public in October 2018). This dataset includes revisions for the years 1988 to 2017 processed by EPA.

total of approximately 274 million pounds of NMP production-related waste. Of this total amount, roughly 245 million pounds were recycled, 7 million pounds were recovered for energy, 10 million pounds were treated, and 10 million pounds were disposed of, or otherwise released to the environment.

Table 1-3. Summary of NMP TRI Production-Related Waste Managed from 2015-2017 (lbs)

Year	Number of Facilities	Recycling	Energy Recovery	Treatment	Releases [a,b,c]	Total Production Related Waste
2015	396	197,244,994	7,129,521	15,607,662	8,824,782	228,806,960
2016	398	193,273,808	7,833,440	14,466,669	10,120,105	225,694,022
2017	380	245,436,619	7,397,866	10,468,156	10,420,124	273,722,765

Data source: 2015-2017 TRI Data (Updated October 2018) (U.S. EPA, 2017f).
[a] Terminology used in these columns may not match the more detailed data element names used in the TRI public data and analysis access points.
[b] Does not include releases due to one-time events not associated with production such as remedial actions or earthquakes.
[c] Counts all releases including release quantities transferred and release quantities disposed of by a receiving facility reporting to TRI.

Table 1-4. provides a summary of NMP releases to the environment reported to TRI for the same reporting years as Table 1-3.[1] Approximately 19,053 pounds of NMP water releases, 1,532,507 pounds of NMP air releases, and roughly 7,548,997 pounds of NMP land releases were reported to TRI in 2017. In addition to the quantities reported as in Table 1-4 as "disposed of in Class I underground injection wells and Resource Conservation and Recovery Act (RCRA) Subtitle C landfills", the reported land disposal techniques included; disposal to landfills other than RCRA Subtitle C (1,920,162 pounds), Class II-V underground injection wells (12,115 pounds), land treatment/application farming (3,571 pounds), RCRA Subtitle C surface impoundments (73 pounds), and other land disposal such as waste piles, spills and leaks (12,521 pounds).[2]

Table 1-4. Summary of NMP TRI Releases to the Environment from 2015-2017 (lbs)

Year	Number of Facilities	Air Releases		Water Releases	Land Disposal			Other Releases [a]	Total On- and Off-Site Disposal or Other Releases [b, c]
		Stack Air Releases	Fugitive Air Releases		Class I Under-ground Injection	RCRA Subtitle C Landfills	All other Land Disposal [a]		
2015	396	887,309	546,060	14,092	3,625,939	93,217	2,737,671	228,099	8,132,388 [d]
		1,433,370 [d]			6,456,827 [d]				
2016	398	1,179,654	571,314	14,861	4,865,286	118,134	2,401,377	283,784	9,434,409 [d]
		1,750,967 [d]			7,384,797 [d]				
2017	380	1,110,652	421,856	19,053	5,243,982	356,574	1,948,441	456,316	9,556,874 [d]
		1,532,507 [d]			7,548,997 [d]				

Data source: 2015-2017 TRI Data (Updated October 2018) (U.S. EPA, 2017f).
[a] Terminology used in these columns may not match the more detailed data element names used in the TRI public data and analysis access points.

[2] Other releases of NMP as shown in Table 1-4 include quantities transferred to a waste broker off-site for disposal (257,614 pounds), storage of NMP off-site (33,000 pound), other off-site management of NMP (14,039 pounds), and unknown off-site waste management practices (151,664 pounds).

[b] These release quantities do include releases due to one-time events not associated with production such as remedial actions or earthquakes.
[c] Counts release quantities once at final disposition, accounting for transfers to other TRI reporting facilities that ultimately dispose of the chemical waste.
[d] Value shown may be different than the summation of individual data elements due to decimal rounding.

While production-related waste managed shown in Table 1-3 excludes any quantities reported as catastrophic or one-time releases (TRI section 8 data), release quantities shown in Table 1-4 include both production-related and non-routine quantities (TRI section 5 and 6 data) for 2015-2017. As a result, release quantities may differ slightly and may further reflect differences in TRI calculation methods for reported release range estimates (U.S. EPA, 2017f).

1.3 Regulatory and Assessment History

EPA conducted a search of existing domestic and international laws, regulations and assessments pertaining to NMP. EPA compiled the summary information provided in Table 1-5 from data available from federal, state, international and other government sources, as cited in Appendix A.

Federal Laws and Regulations

NMP is subject to federal statutes or regulations, other than TSCA, that are implemented by other federal agencies/departments. A summary of federal laws, regulations and implementing authorities is provided in Appendix A.1

State Laws and Regulations

NMP is subject to state statutes or regulations. A summary of state laws, regulations and implementing authorities is provided in Appendix A.2.

Laws and Regulations in Other Countries and International Treaties or Agreements

NMP is subject to statutes or regulations in countries other than the United States and/or international treaties and/or agreements. A summary of these laws, regulations, treaties and/or agreements is provided in Appendix A.3.

EPA identified previous assessments conducted by other organizations (see Table 1-5). Depending on the source, these assessments may include information on conditions of use, hazards, exposures and potentially exposed or susceptible subpopulations.

Table 1-5. Assessment History of NMP

Authoring Organization	Assessment
EPA Assessments	
U.S. EPA, Office of Pollution Prevention and Toxics (OPPT)	TSCA Work Plan Chemical Risk Assessment N-Methylpyrrolidone: Paint Stripping Use CASRN 872-50-4 (U.S. EPA, 2015)
U.S. EPA, OPPT	Re-assessment of Pesticide Inert Ingredient Exemption under the Food Quality Protection Act (U.S. EPA, 2006b)

Authoring Organization	Assessment
Other U.S.-Based Organizations	
California Office of Environmental Health Hazard Assessment (OEHHA)	Proposition 65 Maximum Allowable Dose Level for Reproductive Toxicity (OEHHA, 2003)
International	
National Industrial Chemicals Notification and Assessment Scheme (NICNAS), Australian Government	Human Health Tier III assessment (NICNAS, 2013)
Government of Canada, Environment Canada, Health Canada	Draft Screening Assessment of Risks to Human and Ecological Receptors (Environment Canada, 2017)
European Commission (EC), Scientific Committee on Occupational Exposure Limits (OELs)	Evaluation of Occupational Exposure Limits for NMP (EC, 2016)
Organisation for Economic Co-operation and Development (OECD), Cooperative Chemicals Assessment Program	NMP: SIDS Initial Assessment Profile (OECD, 2007b)
World Health Organization (WHO) International Programme on Chemical Safety (IPCS)	Concise International Chemical Assessment Document 35 N-METHYLPYRROLIDONE (WHO, 2001)
Danish Ministry of the Environment Environmental Protection Agency	Survey of NMP - Miljøstyrelsen (Danish Ministry of the Environment, 2015)

1.4 Scope of the Evaluation

1.4.1 Conditions of Use Included in the Draft Risk Evaluation

TSCA (U.S.C. § 3(4)) defines the conditions of use as ‘‘the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of.” The conditions of use are described below in Table 1-6.

Use categories include the following: “industrial use” means use at a site at which one or more chemicals or mixtures are manufactured (including imported) or processed; “commercial use” means the use of a chemical or a mixture containing a chemical (including as part of an article) in a commercial enterprise providing saleable goods or services; “consumer use” means the use of a chemical or a mixture containing a chemical (including as part of an article, such as furniture or clothing) when sold to or made available to consumers for their use (U.S. EPA, 2017c).

To understand conditions of use relative to one another and associated potential exposures under those conditions of use, Figure 1-1 depicts the life cycle diagram and includes the production volume associated with each stage of the life cycle, as reported in the 2016 CDR reporting (U.S. EPA, 2017c); however, the life cycle diagram for NMP does not include specific production volumes because the information was claimed as confidential business information (CBI).

Additional worker monitoring data were provided to EPA during the public comment period for the NMP problem formulation. This information was incorporated into the occupational exposure estimates for semiconductor and electronics manufacturing.

Table 1-6. Categories and Subcategories of Conditions of Use Included in the Scope of the Draft Risk Evaluation

Life Cycle Stage	Category [a]	Subcategory [b]	References
Manufacture	Domestic Manufacture	Domestic Manufacture	U.S. EPA (2017c)
	Import	Import	U.S. EPA (2017c)
Processing	Processing as a reactant or intermediate	Intermediate in Plastic Material and Resin Manufacturing and in Pharmaceutical and Medicine Manufacturing	U.S. EPA (2017c), Public comments EPA-HQ-OPPT-2016-0743-0010, EPA-HQ-OPPT-2016-0743-0015, EPA-HQ-OPPT-2016-0743-0017
		Other	U.S. EPA (2017c)
	Incorporated into formulation, mixture or reaction product	Adhesives and sealant chemicals in Adhesive Manufacturing	U.S. EPA (2017c), Market profile EPA-HQ-OPPT-2016-0743, Public comments EPA-HQ-OPPT-2016-0743-0007, EPA-HQ-OPPT-2016-0743-0009, EPA-HQ-OPPT-2016-0743-0011
		Anti-adhesive agents in Printing and Related Support Activities	U.S. EPA (2017c), Market profile EPA-HQ-OPPT-2016-0743
		Paint additives and coating additives not described by other codes in Paint and Coating Manufacturing; and Print Ink Manufacturing	U.S. EPA (2017c), Market profile EPA-HQ-OPPT-2016-0743, Public comments EPA-HQ-OPPT-2016-0743-0007, EPA-HQ-OPPT-2016-0743-0009, EPA-HQ-OPPT-2016-0743-0013
		Plating agents and surface treating agents in Fabricated Metal Product Manufacturing	U.S. EPA (2017c)
	Incorporated into formulation, mixture or reaction product	Processing aids not otherwise listed in Plastic Material and Resin Manufacturing	U.S. EPA (2017c), Public comments EPA-HQ-OPPT-2016-0743-0015, EPA-HQ-OPPT-2016-0743-0017, EPA-HQ-OPPT-2016-0743-0035, EPA-HQ-OPPT-2016-0743-0038

Life Cycle Stage	Category [a]	Subcategory [b]	References
Processing		Solvents (for cleaning or degreasing) in Non-Metallic Mineral Product Manufacturing; Machinery Manufacturing; Plastic Material and Resin Manufacturing; Primary Metal Manufacturing; Soap, Cleaning Compound and Toilet Preparation Manufacturing; Transportation Equipment Manufacturing; All Other Chemical Product and Preparation Manufacturing; Printing and Related Support Activities; Services; Wholesale and Retail Trade	U.S. EPA (2017c), Market profile EPA-HQ-OPPT-2016-0743, Public comments EPA-HQ-OPPT-2016-0743-0010, EPA-HQ-OPPT-2016-0743-0011, EPA-HQ-OPPT-2016-0743-0027, EPA-HQ-OPPT-2016-0743-0028
		Solvents (which become part of product formulation or mixture) in Electrical Equipment, Appliance and Component Manufacturing; Other Manufacturing; Paint and Coating Manufacturing; Print Ink Manufacturing; Soap, Cleaning Compound and Toilet Preparation Manufacturing; Transportation Equipment Manufacturing; All Other Chemical Product and Preparation Manufacturing; Printing and Related Support Activities; Wholesale and Retail Trade	U.S. EPA (2017c), Market profile EPA-HQ-OPPT-2016-0743, Public comments EPA-HQ-OPPT-2016-0743-0007, EPA-HQ-OPPT-2016-0743-0009, EPA-HQ-OPPT-2016-0743-0010, EPA-HQ-OPPT-2016-0743-0011, EPA-HQ-OPPT-2016-0743-0019, EPA-HQ-OPPT-2016-0743-0024, EPA-HQ-OPPT-2016-0743-0031, EPA-HQ-OPPT-2016-0743-0034
Processing	Incorporated into formulation,	Surface active agents in Soap, Cleaning Compound and Toilet Preparation Manufacturing	U.S. EPA (2017c), Market profile EPA-HQ-OPPT-2016-0743

Life Cycle Stage	Category [a]	Subcategory [b]	References
	mixture or reaction product	Other uses in Oil and Gas Drilling, Extraction and Support Activities; Plastic Material and Resin Manufacturing; Services	U.S. EPA (2017c), Market profile EPA-HQ-OPPT-2016-0743, Public comment EPA-HQ-OPPT-2016-0743-0016
	Incorporated into article	Lubricants and lubricant additives in Machinery Manufacturing	U.S. EPA (2017c), Market profile EPA-HQ-OPPT-2016-0743
		Paint additives and coating additives not described by other codes in Transportation Equipment Manufacturing	U.S. EPA (2017c)
		Solvents (which become part of product formulation or mixture), including in Textiles, Apparel and Leather Manufacturing	U.S. EPA (2017c), Market profile EPA-HQ-OPPT-2016-0743, Public comment EPA-HQ-OPPT-2016-0743-0027
		Other, including in Plastic Product Manufacturing	U.S. EPA (2017c), Market profile EPA-HQ-OPPT-2016-0743; EPA-HQ-OPPT-2016-0743-0067
	Repackaging	Wholesale and Retail Trade	U.S. EPA (2017c)
	Recycling	Recycling	U.S. EPA (2017f), U.S. EPA (2017c), Public comments EPA-HQ-OPPT-2016-0743-0017, EPA-HQ-OPPT-2016-0743-0031
Distribution in commerce	Distribution	Distribution in Commerce	U.S. EPA (2017f), U.S. EPA (2017c); Use document EPA-HQ-OPPT-2016-0743-0003
Industrial commercial and consumer use	Paints and coatings	Paint and coating removers	U.S. EPA (2017c), Market profile EPA-HQ-OPPT-2016-0743, Public comments EPA-HQ-OPPT-2016-0743-0008, EPA-HQ-OPPT-2016-0743-0010, EPA-HQ-OPPT-2016-0743-0011, EPA-HQ-OPPT-2016-0743-0018, EPA-HQ-OPPT-2016-

Life Cycle Stage	Category [a]	Subcategory [b]	References
			0743-0023, EPA-HQ-OPPT-2016-0743-0025, EPA-HQ-OPPT-2016-0743-0035
		Adhesive removers	Market profile EPA-HQ-OPPT-2016-0743, Public comments EPA-HQ-OPPT-2016-0743-0011, EPA-HQ-OPPT-2016-0743-0018
		Lacquers, stains, varnishes, primers and floor finishes	Market profile EPA-HQ-OPPT-2016-0743, Public comments EPA-HQ-OPPT-2016-0743-0018, EPA-HQ-OPPT-2016-0743-0032, EPA-HQ-OPPT-2016-0743-0035
		Powder coatings (surface preparation)	Market profile EPA-HQ-OPPT-2016-0743, Public comments EPA-HQ-OPPT-2016-0743-0016
	Paint additives and coating additives not described by other codes Paint additives and coating additives not described by other codes	Use in Computer and Electronic Product Manufacturing, Construction, Fabricated Metal Product Manufacturing, Machinery Manufacturing, Other Manufacturing, Paint and Coating Manufacturing, Primary Metal Manufacturing, Transportation Equipment Manufacturing, Wholesale and Retail Trade	U.S. EPA (2017c), Public comments EPA-HQ-OPPT-2016-0743-0006, EPA-HQ-OPPT-2016-0743-0007, EPA-HQ-OPPT-2016-0743-0009, EPA-HQ-OPPT-2016-0743-0011, EPA-HQ-OPPT-2016-0743-0013, EPA-HQ-OPPT-2016-0743-0018, EPA-HQ-OPPT-2016-0743-0019, EPA-HQ-OPPT-2016-0743-0023, EPA-HQ-OPPT-2016-0743-0024, EPA-HQ-OPPT-2016-0743-0027, EPA-HQ-OPPT-2016-0743-0031, EPA-HQ-OPPT-2016-0743-0032, EPA-HQ-OPPT-2016-0743-0035, EPA-HQ-OPPT-2016-0743-0036, EPA-HQ-OPPT-2016-0743-0063; EPA-HQ-OPPT-2016-0743-0064

Life Cycle Stage	Category [a]	Subcategory [b]	References
Industrial commercial and consumer use	Solvents (for cleaning or degreasing)	Use in Electrical Equipment, Appliance and Component Manufacturing.	U.S. EPA (2017c), Public comments EPA-HQ-OPPT-2016-0743-0006, EPA-HQ-OPPT-2016-0743-0007, EPA-HQ-OPPT-2016-0743-0009, EPA-HQ-OPPT-2016-0743-0023, EPA-HQ-OPPT-2016-0743-0024, EPA-HQ-OPPT-2016-0743-0027
	Ink, toner and colorant products	Printer ink	U.S. EPA (2017c), Use document, EPA-HQ-OPPT-2016-0743-0003, Public comments EPA-HQ-OPPT-2016-0743-0006, EPA-HQ-OPPT-2016-0743-0016, EPA-HQ-OPPT-2016-0743-0018
		Inks in writing equipment	U.S. EPA (2017c), Market profile EPA-HQ-OPPT-2016-0743, Public comment EPA-HQ-OPPT-2016-0743-0018
	Processing aids, specific to petroleum production	Petrochemical Manufacturing	U.S. EPA (2017c), Public comment, EPA-HQ-OPPT-2016-0743-0031
	Adhesives and sealants	Adhesives and sealant chemicals including binding agents	U.S. EPA (2017c), Market profile EPA-HQ-OPPT-2016-0743, Public comments EPA-HQ-OPPT-2016-0743-0006, EPA-HQ-OPPT-2016-0743-0007, EPA-HQ-OPPT-2016-0743-0011, EPA-HQ-OPPT-2016-0743-0016, EPA-HQ-OPPT-2016-0743-0018, EPA-HQ-OPPT-2016-0743-0023
Industrial commercial and consumer use	Adhesives and sealants	Single component glues and adhesives, including lubricant adhesives	U.S. EPA (2017c), Market profile EPA-HQ-OPPT-2016-0743, Public comments EPA-HQ-OPPT-2016-0743-0011, EPA-HQ-OPPT-2016-0743-0018, EPA-HQ-OPPT-2016-0743-0035, EPA-HQ-OPPT-2016-0743-0036

Life Cycle Stage	Category [a]	Subcategory [b]	References
		Two-component glues and adhesives, including some resins	U.S. EPA (2017c), Market profile EPA-HQ-OPPT-2016-0743, Public comments EPA-HQ-OPPT-2016-0743-0011, EPA-HQ-OPPT-2016-0743-0016, EPA-HQ-OPPT-2016-0743-0018
	Other uses	Soldering materials	Market profile EPA-HQ-OPPT-2016-0743, Public comments EPA-HQ-OPPT-2016-0743-0023
		Anti-freeze and de-icing products	U.S. EPA (2017c)
		Automotive care products	U.S. EPA (2017c), Public comment, EPA-HQ-OPPT-2016-0743-0035
		Lubricants and greases	U.S. EPA (2017c)
		Metal products not covered elsewhere	U.S. EPA (2017c), Public comment, EPA-HQ-OPPT-2016-0743-0027, EPA-HQ-OPPT-2016-0743-0028 Public comment, EPA-HQ-OPPT-2016-0743-0027, EPA-HQ-OPPT-2016-0743-0028
		Laboratory chemicals	U.S. EPA (2017c), Public comments EPA-HQ-OPPT-2016-0743-0007, EPA-HQ-OPPT-2016-0743-0009
Industrial commercial and consumer use	Other uses	Lithium ion batteries	Market profile EPA-HQ-OPPT-2016-0743, Public comment EPA-HQ-OPPT-2016-0743-0005
		Cleaning and furniture care products, including wood cleaners, gasket removers	Market profile EPA-HQ-OPPT-2016-0743, Public comment EPA-HQ-OPPT-2016-0743-0025, EPA-HQ-OPPT-2016-0743-0035
		Other uses in Oil and Gas Drilling, Extraction and Support Activities [c]	U.S. EPA (2017c),
		Lubricant and lubricant additives, including hydrophilic coatings	Market profile EPA-HQ-OPPT-2016-0743

Life Cycle Stage	Category [a]	Subcategory [b]	References
		Fertilizer and other agricultural chemical manufacturing - processing aids and solvents	U.S. EPA (2017c), Public comment EPA-HQ-OPPT-2016-0743-0010, EPA-HQ-OPPT-2016-0743-0036
		Pharmaceutical and Medicine Manufacturing - functional fluids (closed systems)	U.S. EPA (2017c), Public comment EPA-HQ-OPPT-2016-0743-0031
		Wood preservatives	Market profile EPA-HQ-OPPT-2016-0743, Public comment EPA-HQ-OPPT-2016-0743-0023
		Industrial pre-treatment	U.S. EPA (2017f)
Disposal	Disposal	Industrial wastewater treatment	U.S. EPA (2017f)
		Publicly owned treatment works (POTW)	U.S. EPA (2017f)
		Underground injection	U.S. EPA (2017f), Public comment EPA-HQ-OPPT-2016-0743-0031
		Landfill (municipal, hazardous or other land disposal)	U.S. EPA (2017f), Public comment EPA-HQ-OPPT-2016-0743-0031
		Emissions to air	
		Incinerators (municipal and hazardous waste)	

[a] These categories of conditions of use appear in the life cycle diagram, reflect CDR codes and broadly represent NMP conditions of use in industrial and/or commercial settings.
[b] These subcategories reflect more specific uses of NMP.
[c] Industrial use added to reflect the use of NMP in products in the Oil and Gas Drilling, Extraction This addition to the risk evaluation will help ensure that EPA determines whether NMP presents an unreasonable risk "under the conditions of use," TSCA 6(b)(4)(A).

509

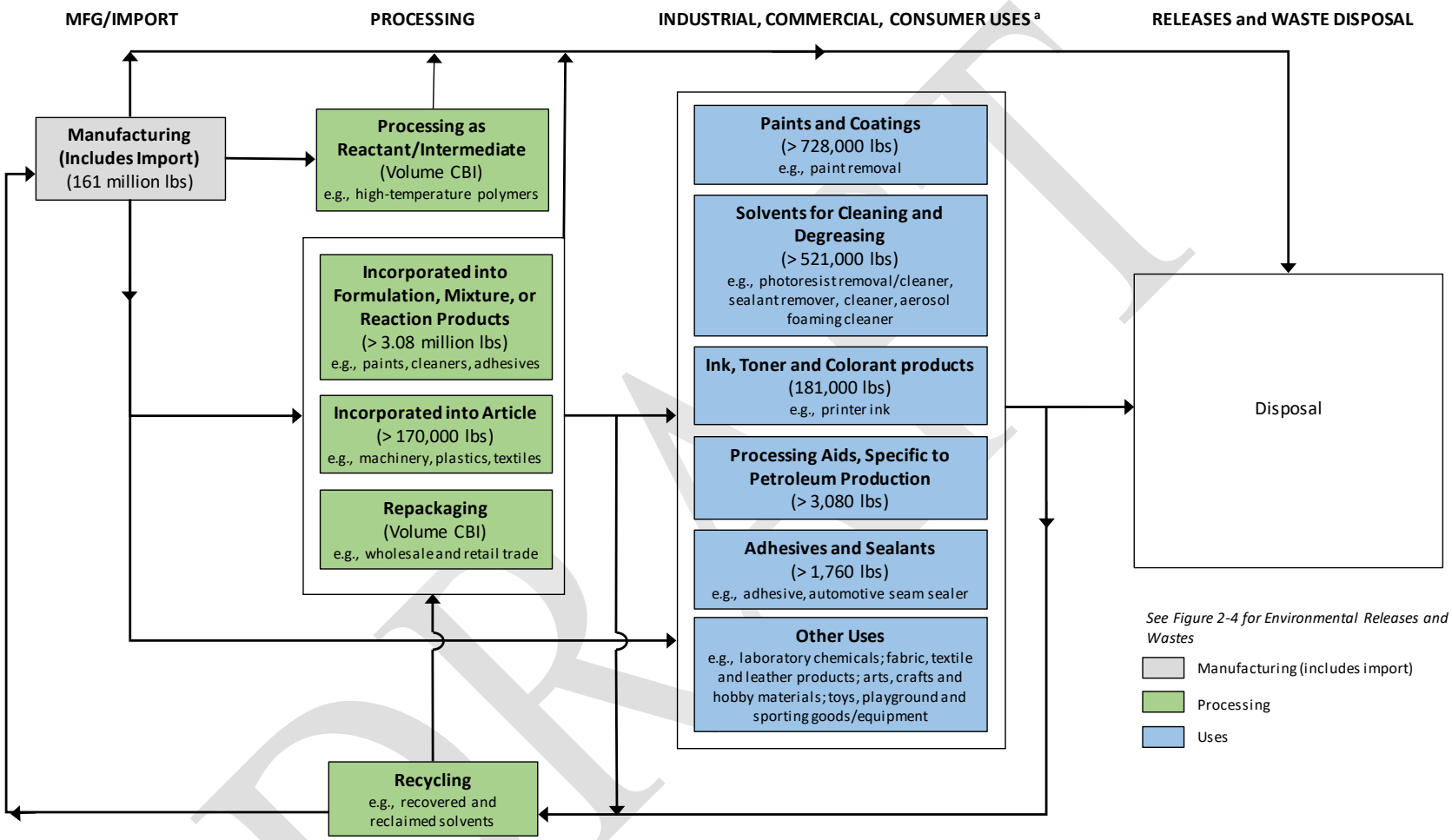


Figure 1-1. NMP Life Cycle Diagram

The life cycle diagram depicts the conditions of use that are considered within the scope of the draft risk evaluation during various life cycle stages including manufacturing, processing, distribution, use and disposal. The production volumes shown are for reporting year 2015 from the 2016 CDR reporting period (U.S. EPA, 2017c). Activities related to distribution (e.g., loading, unloading) will be considered throughout the NMP life cycle, rather than using a single distribution scenario.

[a] See Table 1-6 for additional uses not mentioned specifically in this diagram.

1.4.2 Conceptual Model

EPA considered the hazards that may result from exposure pathways outlined in the preliminary conceptual models of the NMP Scope document (U.S. EPA, 2017d). These conceptual models considered potential exposures resulting from consumer activities and uses, industrial and commercial activities, environmental releases and waste disposal. During problem formulation EPA modified the initial conceptual models provided in the NMP Scope document based on reasonably available information identified for NMP (U.S. EPA, 2018c). For reasons described below, the oral route of exposure was removed from the conceptual model for consumer activities and uses.

During risk evaluation, EPA considered oral exposures that may result from consumer use of NMP-containing products (e.g., infant mouthing behaviors). EPA reviewed experimental product-testing information on NMP content in consumer articles and determined which products are likely to be mouthed (e.g., blankets, toys). EPA then identified information sources that measured NMP content in various consumer products and considered additional contextual information regarding product use, including the extent of NMP migration from these products. Based on this information, the potential for consumer exposure via the oral route is expected to be negligible; therefore, this exposure pathway will not be further analyzed.

The conceptual model presented in the NMP Problem Formulation also listed dust as potential NMP exposure pathway for consumers. There is limited information available on NMP levels in dust, but EPA expects the impacts of this uncertainty to be negligible, as this exposure source is encompassed within the conservative estimates derived for dermal and inhalation exposures (Environment Canada, 2017).

Lastly, EPA did analyze NMP exposures to bystanders (i.e., those located near consumers during use) who do not have direct contact with NMP-containing consumer products. Though EPA's 2015 Paint Remover risk assessment showed no risks to bystanders from indirect exposure to NMP air concentrations associated with consumer use, the supplemental paint remover analysis in the risk assessment consisted of several scenarios resulting in high NMP air concentrations that could expose other individuals in the home (see 6F.2) (U.S. EPA, 2015). Given the evaluation of a greater number of conditions of use in addition to paint removers, EPA estimated NMP exposures to bystanders.

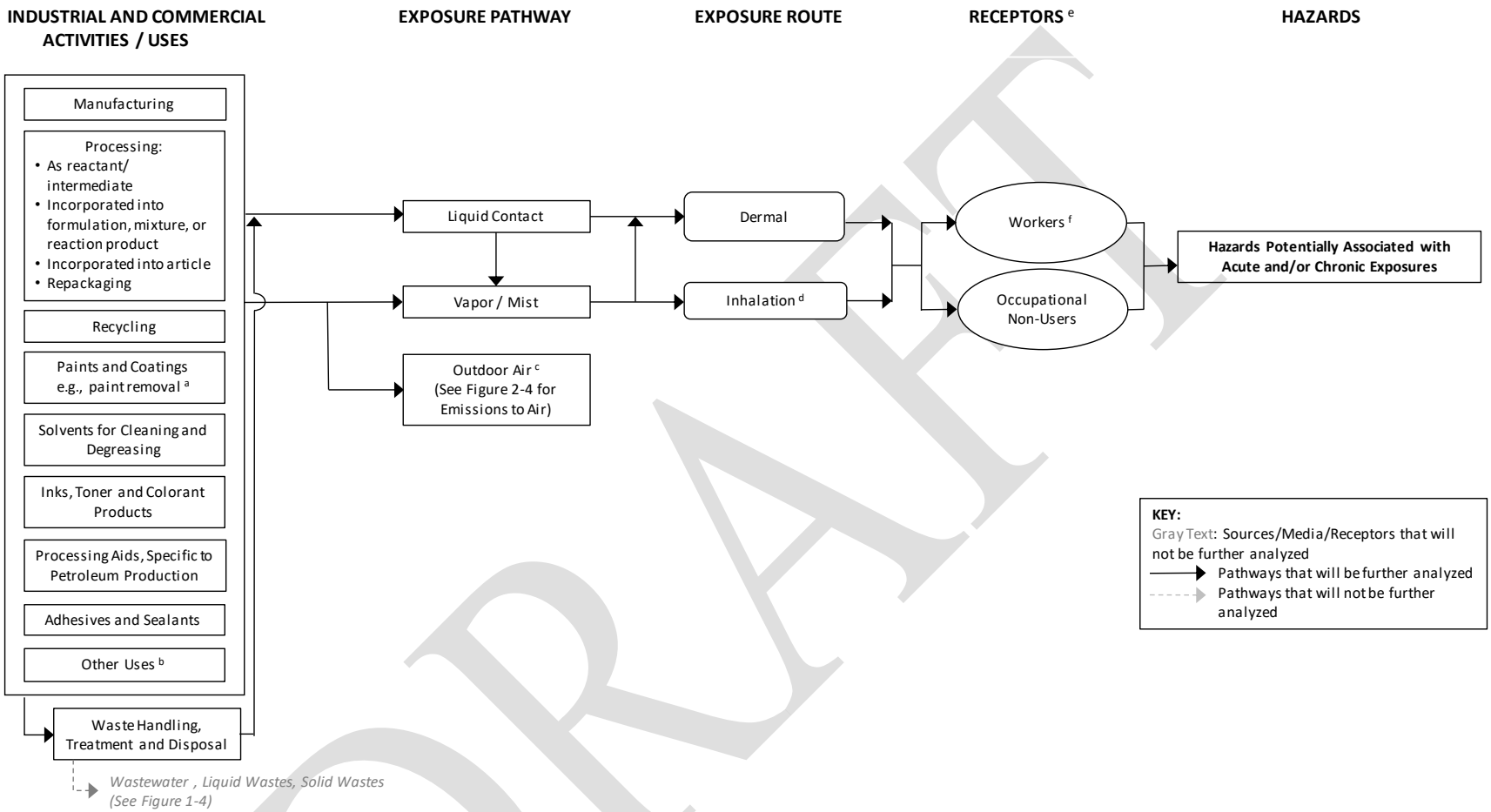


Figure 1-2. NMP Conceptual Model for Industrial and Commercial Activities and Uses: Potential Exposures and Hazards

The conceptual model presents exposure pathways, routes and hazards to human receptors from industrial and commercial uses of NMP.

[a] U.S. EPA (2015) assessed NMP use in paint removal; these uses will be considered during risk evaluation to ensure previous assessments are aligned with the Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act (40 CFR Part 702).

[b] Some products are used in both commercial and consumer applications. Additional uses of NMP are included in Table 1-6.

[c] Emissions to outdoor air include stack emissions and fugitive emissions such as fugitive equipment leaks from valves, pump seals, flanges, compressors, sampling connections and open-ended lines; evaporative losses from surface impoundment and spills; and releases from building ventilation systems.

[d] Oral exposure via incidental ingestion of inhaled vapor/mist will be considered as an inhalation exposure.

[e] Receptors include potentially exposed or susceptible subpopulations.

[f] When data and information are available to support the analysis, EPA expects to consider the effect that engineering controls and/or personal protective equipment have on occupational exposure levels.

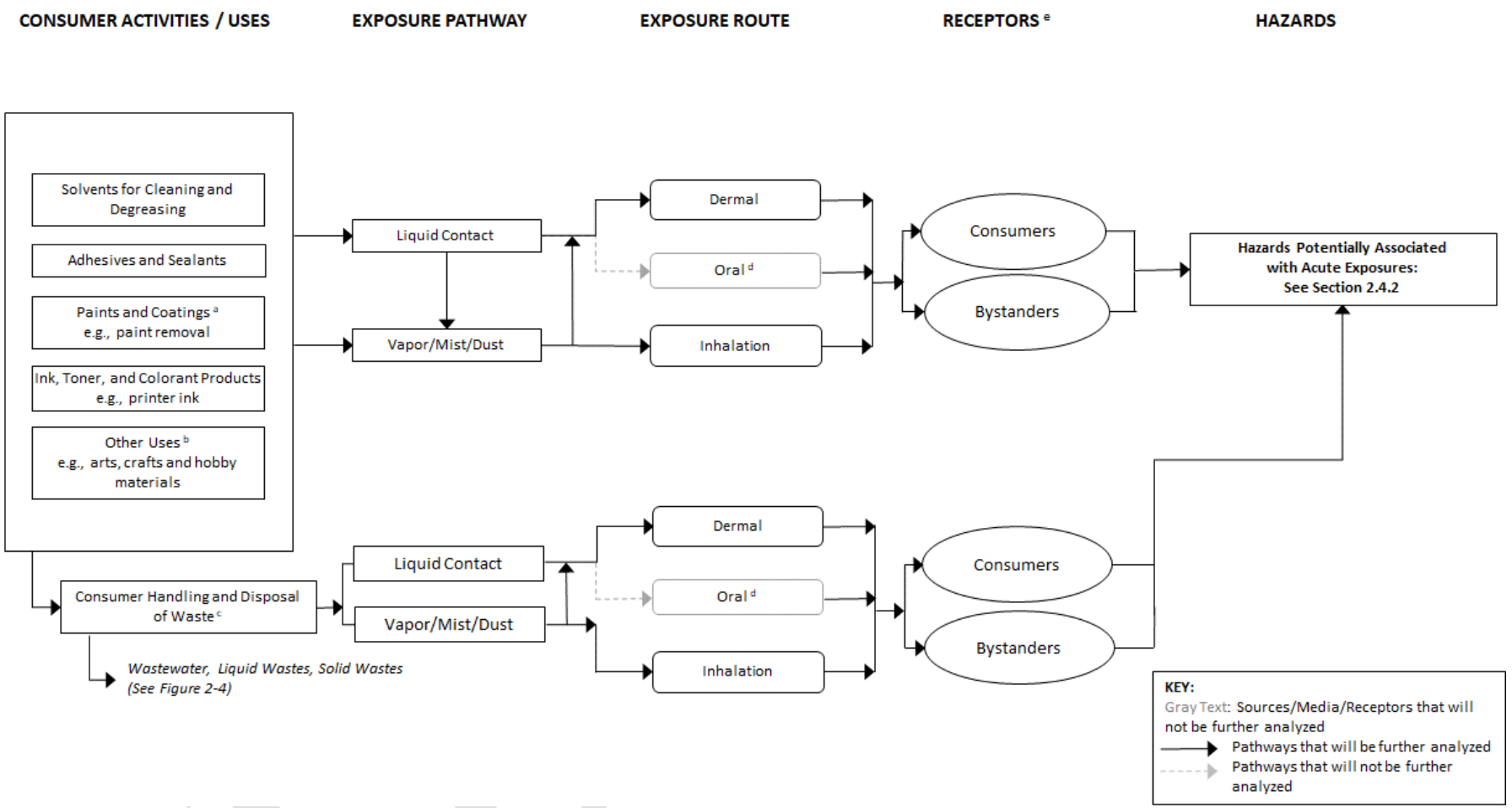


Figure 1-3. NMP Conceptual Model for Consumer Activities and Uses: Potential Exposures and Hazards

The conceptual model presents the exposure pathways, routes and hazards to human receptors from consumer activities and uses of NMP.

[a] U.S. EPA (2015) assessed NMP use in paint and coating removal; these uses will be considered during risk evaluation to ensure previous assessments are aligned with the Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act (40 CFR Part 702).

[b] Some products are used in both commercial and consumer applications; additional uses of NMP are included in Table 1-6.

[c] Consumers may also be exposed while handling municipal wastes; however, the pathway is uncertain.

[d] Oral exposure via incidental ingestion of inhaled vapor/mist/dust will be considered as an inhalation exposure.

[e] Receptors include potentially exposed or susceptible subpopulations.

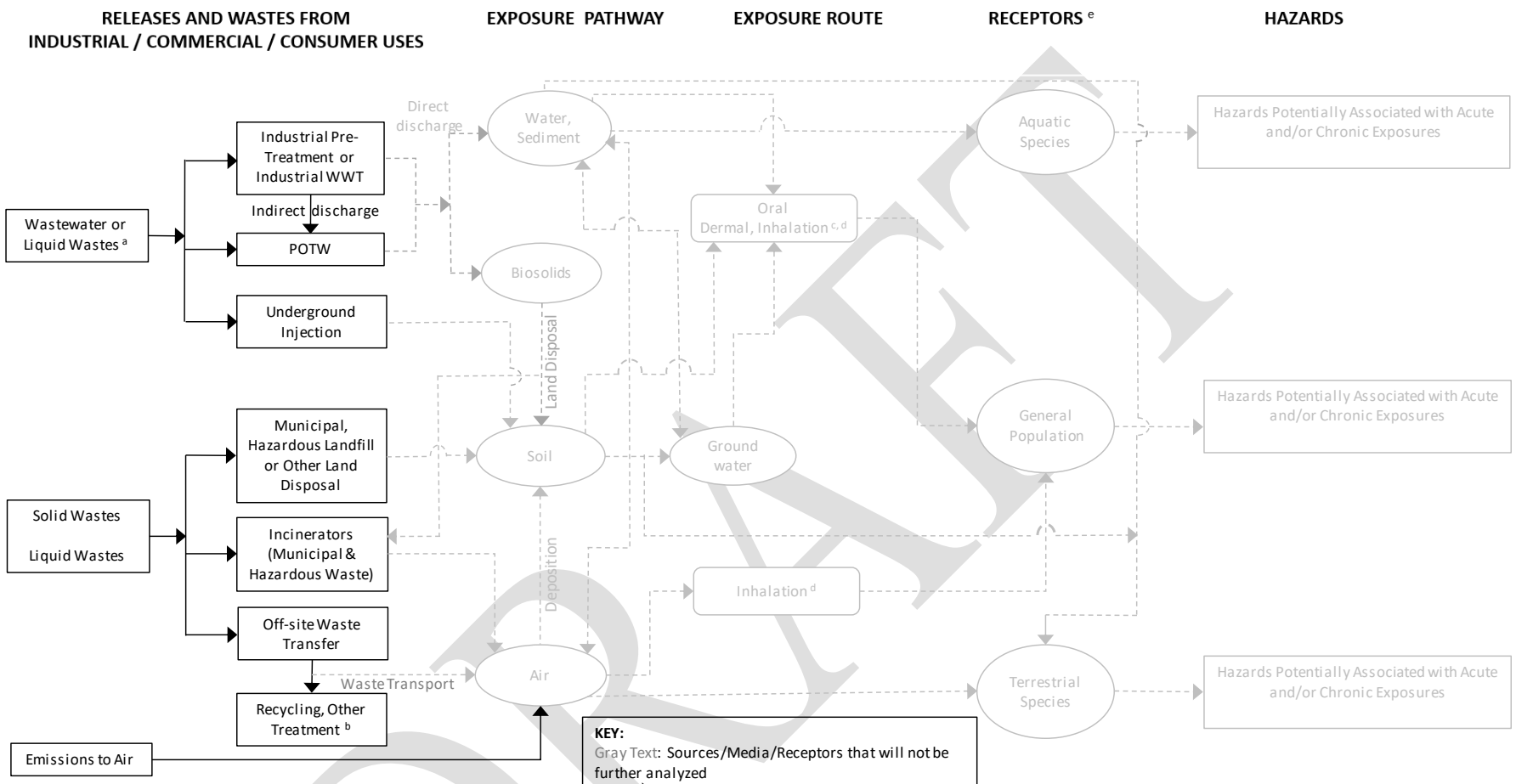


Figure 1-4. NMP Conceptual Model for Environmental Releases and Wastes: Potential Exposures and Hazards

The conceptual model presents the exposure pathways, routes and hazards to human and environmental receptors from NMP environmental releases.

[a] Industrial wastewater or liquid wastes may be treated on-site and then released to surface water (direct discharge), or pre-treated and released to POTW (indirect discharge). For consumer uses, such wastes may be released directly to POTW (i.e., down the drain). Drinking water will undergo further treatment in drinking water treatment plant. Ground water may also be a source of drinking water.

[b] Additional releases may occur from recycling and other waste treatment.

[c] Volatilization from or contact with NMP-containing drinking/tap water during showering, bathing and washing represents another potential exposure pathway.

[d] Presence of mist is unlikely; inhalation and oral exposure are expected to be negligible.

[e] Receptors include potentially exposed or susceptible subpopulations.

582 EPA did not include pathways under programs of other environmental statutes, administered by
583 EPA for which long-standing regulatory and analytical processes already exist. For example,
584 EPA does not consider on-site NMP land releases that are disposed via underground injection in
585 the risk evaluation. Most of the on-site land disposal reported for NMP in the 2015 TRI was to
586 Class I underground injection wells (approximately 3.6 million pounds), with no reported
587 environmental releases via underground injection to Class II-VI wells (U.S. EPA, 2017c).
588 Environmental disposal of NMP via injection into Class I wells is managed and prevented from
589 further environmental releases by RCRA and Safe Drinking Water Act (SDWA) regulations.
590 Therefore, disposal of NMP via underground injection is not likely to result in environmental
591 and general population exposures.

592 During problem formulation, EPA used information reported in EPA's Toxics Release Inventory
593 (TRI) to predict NMP surface water concentrations near facilities reporting the largest discharges
594 to water. NMP surface water concentrations were estimated using conservative assumptions with
595 EPA's Exposure and Fate Assessment Screening Tool, Version 2014 (E-FAST 2014). TRI water
596 releases for the top 12 facilities reporting NMP releases and the associated estimates of NMP
597 surface water concentrations estimated in the NMP Problem Formulation (U.S. EPA, 2018c) are
598 shown in Appendix D.

599 EPA identified a low risk concern for NMP exposure to aquatic organisms based on the TRI
600 reported discharges of NMP to surface waters. To capture "high-end" surface water
601 concentrations, EPA compiled the release data for six facilities that reported the largest NMP
602 direct water releases. This represented > 99% of the total volume of NMP reported as a direct
603 discharge to surface water during the 2015 TRI reporting period. Comparing these "high-end"
604 surface water concentrations with the respective concentrations of concern identified for aquatic
605 organisms indicate a low risk concern (see Table 4-1). EPA does not anticipate a risk concern for
606 environmental receptors from NMP releases to surface water.
607

1.5 Systematic Review

TSCA requires EPA to use scientific information, technical procedures, measures, methods, protocols, methodologies and models consistent with the best available science and base decisions under Section 6 on the weight of scientific evidence. Within the TSCA risk evaluation context, the weight of the scientific evidence is defined as "*a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance*" (40 C.F.R. 702.33).

To meet the TSCA § 26(h) science standards, EPA used the TSCA systematic review process described in the *Application of Systematic Review in TSCA Risk Evaluations* document (U.S. EPA, 2018a). The process complements the risk evaluation process in that the data collection, data evaluation, and data integration stages of the systematic review process are used to develop the exposure and hazard assessments based on reasonably available information. EPA defines "reasonably available information" to mean information that EPA possesses, or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation (40 C.F.R. 702.33).

EPA is implementing systematic review methods and approaches within the regulatory context of the amended TSCA. Although EPA will make an effort to adopt as many best practices as practicable from the systematic review community, EPA expects modifications to the process to ensure that the identification, screening, evaluation and integration of data and information can support timely regulatory decision making under the aggressive timelines of the statute.

1.5.1 Data and Information Collection

EPA planned and conducted a comprehensive literature search based on key words related to the discipline-specific evidence supporting the risk evaluation (e.g., environmental fate and transport; engineering releases and occupational exposure; exposure to general population, consumers and environmental exposure; and environmental and human health hazards). EPA then developed and applied inclusion and exclusion criteria during the title and abstract screening to identify information potentially relevant for the risk evaluation process. The literature and screening strategy as specifically applied to NMP is described in the *Strategy for Conducting Literature Searches for NMP: Supplemental File to the TSCA Scope document* (U.S. EPA, 2017e); results of the title and abstract screening process are published in the *N-Methylpyrrolidone (CASRN 872-50-4) Bibliography: Supplemental File to the TSCA Scope Document* (U.S. EPA, 2017b).

For studies determined to be on-topic after title and abstract screening, EPA conducted a full text screening to further exclude references that were not relevant to the risk evaluation. Screening decisions were made based on eligibility criteria documented in the form of the populations,

exposures, comparators, and outcomes (PECO) framework or a modified framework[3]. Data sources that met the criteria were carried forward to the data evaluation stage. The inclusion and exclusion criteria for full text screening for NMP are available in Appendix G of the NMP Problem Formulation document (U.S. EPA, 2018c).

In addition to the comprehensive literature search and screening process described above, EPA leveraged information presented in previous assessments[4] when identifying relevant key and supporting data[5] and information for developing the NMP draft risk evaluation. This is discussed in the *Strategy for Conducting Literature Searches for NMP: Supplemental Document to the TSCA Scope document* (U.S. EPA, 2017e). In general, many of the key and supporting data sources were identified in the *NMP (CASRN 872-50-4) Bibliography: Supplemental File for the TSCA Scope Document* (U.S. EPA, 2017b). However, there were instances where EPA missed relevant sources that were not captured in the initial categorization of the on-topic references. EPA found additional data and information using backward reference searching, a technique that will be included in future search strategies. This issue was discussed in Section 4 of the *Application of Systematic Review for TSCA Risk Evaluations*(U.S. EPA, 2018a). Other relevant key and supporting studies were identified through targeted supplemental searches conducted to inform the analytical approaches and methods used in the NMP draft risk evaluation (e.g., to identify specific information needed for exposure modeling) or to identify new information published after the date of the initial search.

EPA used previous chemical assessments to quickly identify relevant key and supporting studies in order to expedite the data quality evaluation of these data sources, but many were already captured in the comprehensive literature search strategy described above. EPA also considered newer information not covered by previous chemical assessments, as described in the *Strategy for Conducting Literature Searches for NMP: Supplemental Document to the TSCA Scope document* (U.S. EPA, 2017e). EPA then evaluated the confidence of this information rather than evaluating the confidence of all underlying evidence ever published on NMP fate and transport, environmental releases, and environmental and human exposure and hazard potential. Such a comprehensive evaluation would be extremely labor intensive and could not be achieved under the TSCA statutory deadlines for most chemical substances, especially those that are data rich. EPA also considered how this approach to data evaluation would change the conclusions presented in previous assessments.

Using this pragmatic approach, EPA maximized the scientific and analytical efforts of other regulatory and non-regulatory agencies by accepting for the most part, the relevant scientific

[3] A PESO statement was used during the full text screening of environmental fate and transport data sources. PESO stands for Pathways and Processes, Exposure, Setting or Scenario, and Outcomes. A RESO statement was used during the full text screening of the engineering and occupational exposure literature. RESO stands for Receptors, Exposure, Setting or Scenario, and Outcomes.

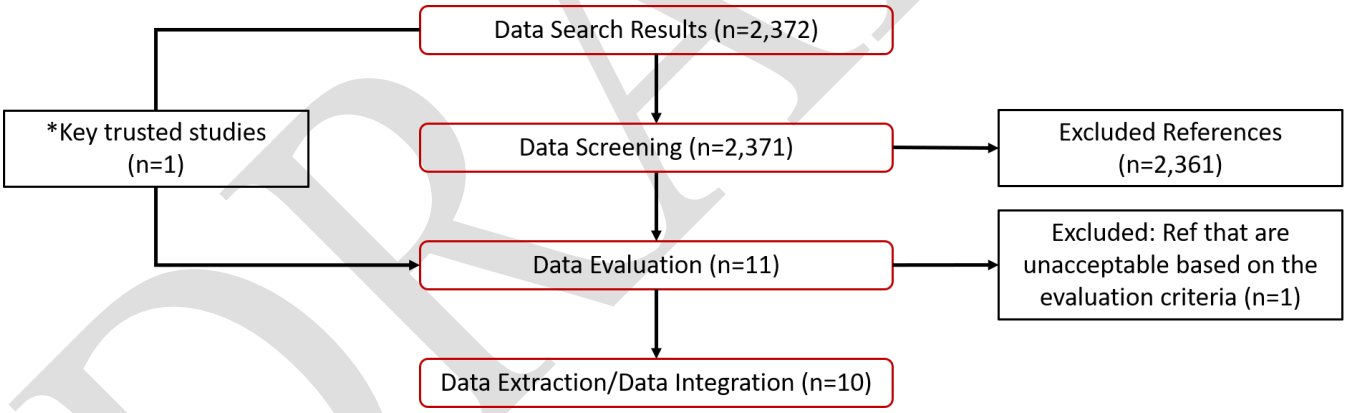
[4] Examples of existing assessments are EPA's chemical assessments (e.g. previous work plan risk assessments, problem formulation documents), ATSDR's Toxicological Profiles, EPA's IRIS assessments and ECHA's dossiers. This is described in more detail in the *Strategy for Conducting Literature Searches for 1,4-Dioxane: Supplemental File for the TSCA Scope Document* (https://www.epa.gov/sites/production/files/2017-06/documents/14-dioxane_lit_search_strategy_053017.pdf).

[5] Key and supporting data and information are those that support key analyses, arguments, and/or conclusions in the risk evaluation.

knowledge gathered and analyzed by others, except for influential information sources that may impact the weight of the scientific evidence underlying EPA's risk findings. This influential information (i.e., key/supporting studies) came from a smaller pool of information sources subjected to the rigor of the TSCA systematic review process to ensure that the best available science is incorporated into the weight of the scientific evidence used to support the NMP draft risk evaluation.

The literature flow diagrams shown in Figures 1-5, 1-6, 1-7, 1-8, and 1-9 highlight the results obtained for each scientific discipline based on this approach. Each diagram provides the total number of references considered at the start of each systematic review stage (i.e., data search, data screening, data evaluation, data extraction/data integration) and those excluded based on the criteria guiding EPA's screening and data quality evaluation decisions.

EPA made the decision to bypass the data screening step for data sources that were highly relevant to the draft risk evaluation as described above. These data sources are depicted as "key/supporting data sources" in the literature flow diagrams. Note that the number of "key/supporting data sources" were excluded from the total count during the data screening stage and added, for the most part, to the data evaluation stage depending on the discipline-specific evidence. The exception was the engineering releases and occupational exposure data sources that were subject to a combined data extraction and evaluation step (Figure 1-6).



*These are key and supporting studies from existing assessments (e.g., EPA IRIS assessments, ATSDR assessments, ECHA dossiers) that were highly relevant for the TSCA risk evaluation. These studies bypassed the data screening step and moved directly to the data evaluation step.

Figure 1-5. Key/Supporting Data Sources for Environmental Fate and Transport

The number of publications considered in each step of the systematic review of the NMP fate and transport literature is summarized in Figure 1-5. Literature on the environmental fate and transport of NMP were gathered and screened as described in *Appendix C of* the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). Additional information regarding the literature search and screening strategy for NMP is provided in EPA's *Strategy for Conducting Literature Searches for N-Methylpyrrolidone (NMP): Supplemental File to the TSCA Scope Document* (U.S. EPA, 2017e). The results of this screening are published in the *NMP*

(CASRN 872-50-4) Bibliography: Supplemental File to the TSCA Scope Document (U.S. EPA, 2017b).

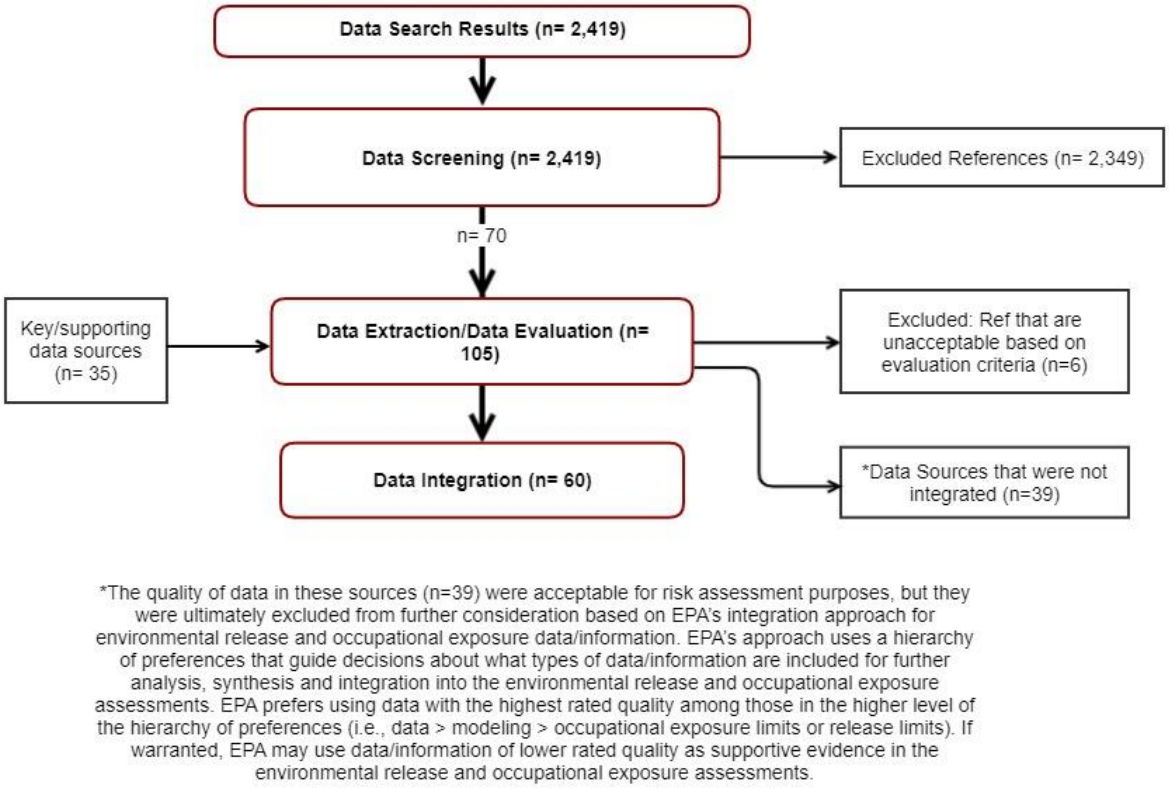


Figure 1-6. Key/Supporting Sources for Releases and Occupational Exposures

As shown in Figure 1-6, the literature search strategy for NMP environmental releases and occupational exposures yielded 2,419 data sources. Of these, 70 data sources were determined to be relevant to the NMP draft risk evaluation during the data screening process. These relevant data sources progressed to the data extraction/evaluation phase. After data extraction/evaluation, EPA identified several data gaps and performed a supplemental, targeted search to fill these gaps (e.g. to locate information needed for exposure modeling). This supplemental search yielded 35 relevant data sources that bypassed the initial data screening step. These new data sources were added to the 70 data sources originally determined to be relevant during the data screening process; all were evaluated and extracted in accordance with the process described in Appendix D of the *Application of Systematic Review in TSCA Risk Evaluations* document (U.S. EPA, 2018a). Of the 105 sources evaluated, 6 were rated as containing only unacceptable data based on serious flaws detected during data evaluation. Of the 99 sources considered for data integration, 39 were not integrated based on EPA's integration approach (i.e., higher quality data were used). Data from the remaining 60 sources were integrated into the NMP draft risk evaluation.

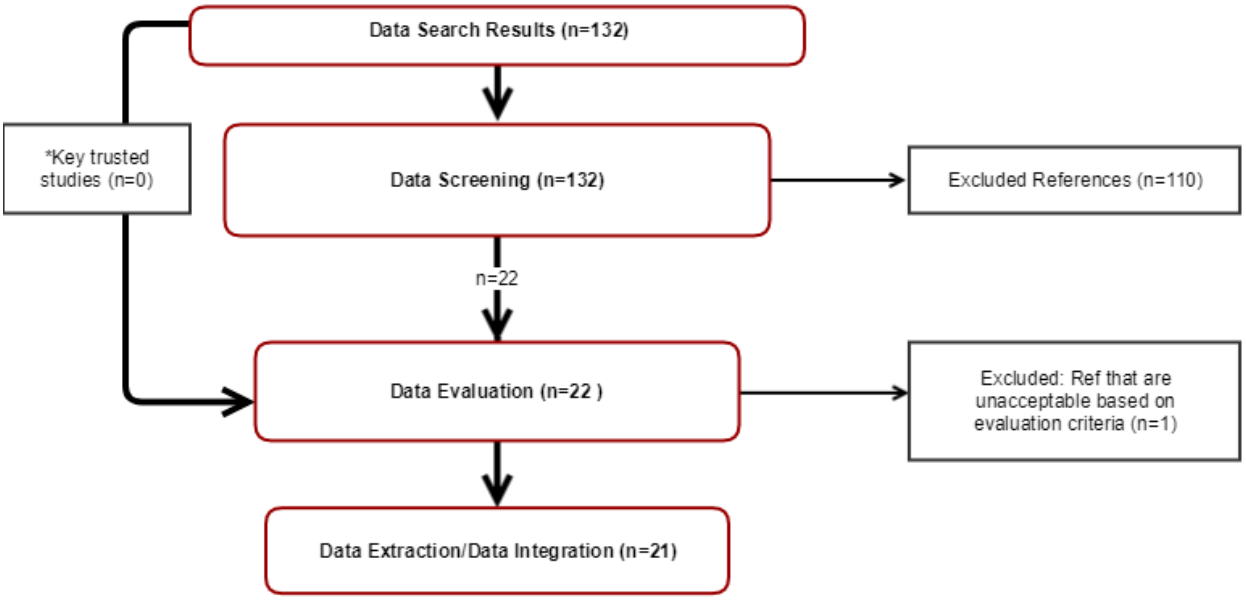


Figure 1-7. Key/Supporting Sources for General Population, Consumer and Environmental Exposures

The number of data and information sources considered in each step of the systematic review of NMP literature on general population, consumer and environmental exposure is summarized in Figure 1-7. The literature search results for general population, consumer and environmental exposures yielded 132 data sources. Of these data sources, 22 were determined to be relevant to the NMP draft risk evaluation through the data screening process. These relevant data sources were evaluated in accordance with *Appendix E of the Application of Systematic Review in TSCA Risk Evaluations* document *(*U.S. EPA, 2018a*).*

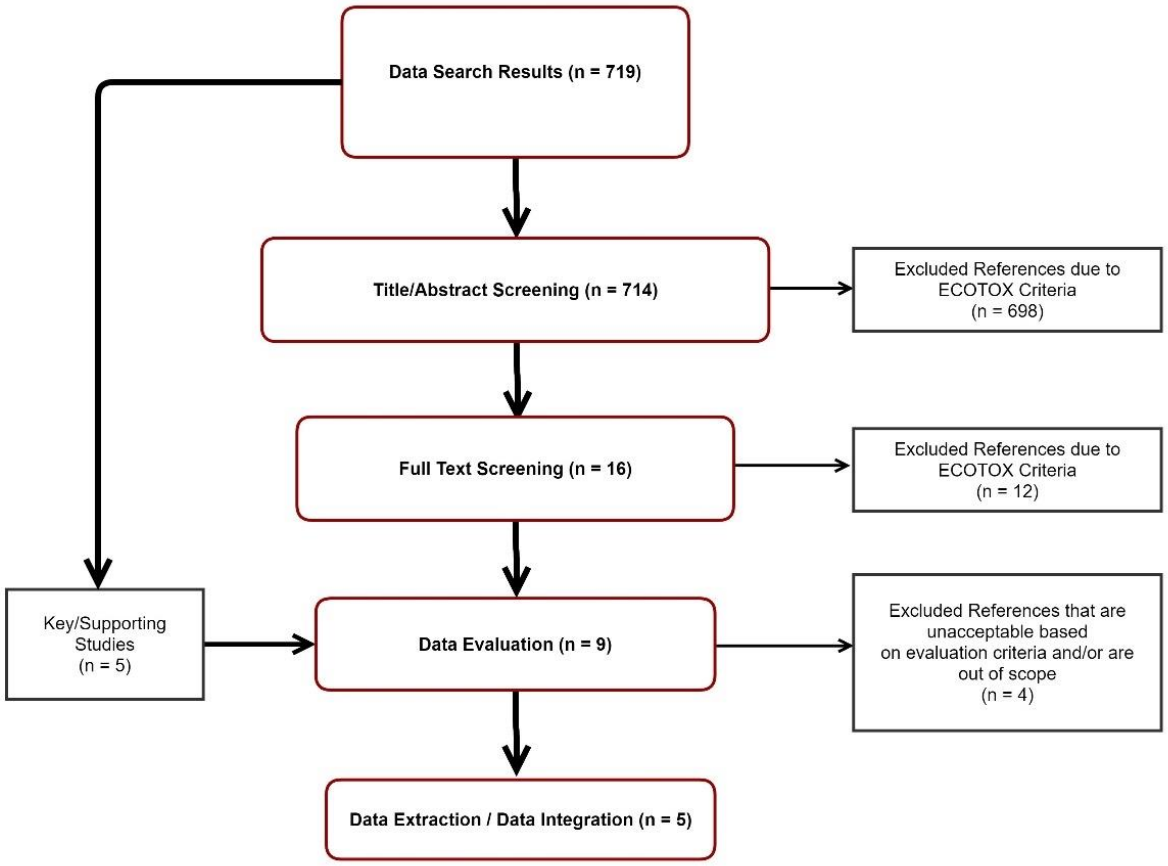


Figure 1-8. Key/Supporting Data Sources for Environmental Hazards

The environmental hazard data sources for NMP were identified through literature searches and screening strategies using the ECOTOXicology knowledgebase system (ECOTOX) Standing Operating Procedures. For studies determined to be on-topic after title and abstract screening, EPA conducted a full text screening to further exclude citations that were not considered relevant to the NMP draft risk evaluation. Screening decisions were made based on eligibility criteria as documented in the ECOTOX User Guide (U.S. EPA, 2018b)). Additional details can be found in the *Strategy for Conducting Literature Searches for NMP: Supplemental Document to the TSCA Scope Document* (U.S. EPA, 2017e).

The literature search strategy for environmental hazard data identified 719 citations for NMP Figure 1-8). At the title and abstract screening phase, 698 of these citations were excluded as "off-topic" based on EPA's ECOTOX knowledgebase criteria. The remaining 16 citations underwent a more thorough (full-text) screening process using the same ECOTOX criteria to determine which should proceed to data evaluation. Several citations were determined to be "out of scope" during the initial screening steps and were therefore excluded from data evaluation. Five "Key/Supporting Citations" for Environmental Hazard were identified by EPA as a result of a review of the OECD HPV SIDS Document for NMP (OECD, 2009b). EPA obtained the full study reports from BASF and GAF (only summaries are provided in the OECD document). Of these five citations, three were translated from German. These five citations were found independently from the ECOTOX process.

EPA developed data quality evaluation criteria based on a combination of EPA's ECOTOXicology knowledgebase (ECOTOX) criteria and the Criteria for Reporting and Evaluating ecotoxicity Data (CRED), as discussed in the *Applications of Systematic Review for TSCA Risk Evaluations* (U.S. EPA, 2018a). Nine citations went through the data evaluation process using the data quality evaluation criteria for NMP. EPA analyzed each individual toxicity study in each of these citations using the data quality evaluation to determine the overall study quality. Four citations were excluded during data evaluation. In total, five citations were evaluated for data extraction/integration in the NMP draft risk evaluation.

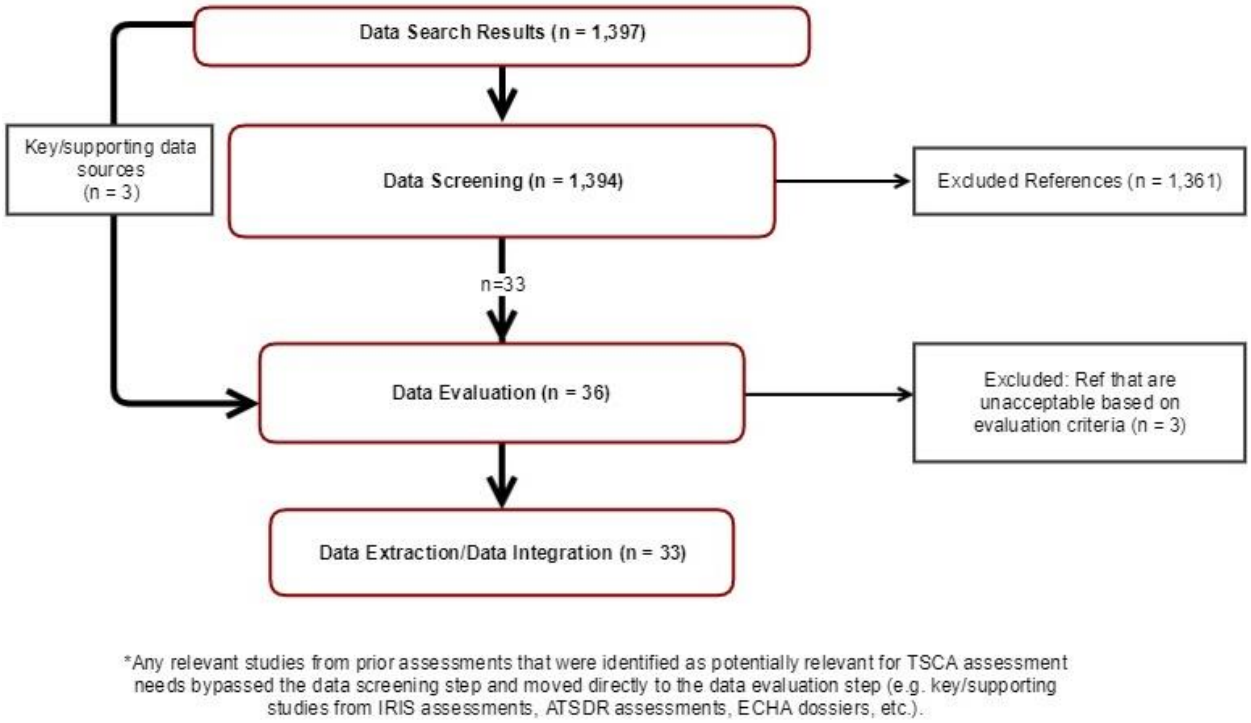


Figure 1-9. Literature Flow Diagram for Human Health Key/Supporting Data Sources

The literature search strategy used to gather human health hazard information for NMP yielded 1,397 studies. This included three key and supporting studies (identified from previous regulatory assessments) that skipped the initial screening process and proceeded directly to the data evaluation phase. Of the 1,394 studies identified for NMP, 1,361 were excluded as off topic during the title and abstract screening phase. The remaining 36 human health hazard studies advanced to full text screening; 33 were determined to be relevant to the NMP draft risk evaluation. These relevant data sources were evaluated and extracted in accordance with the process described in *Appendix G of the Application of Systematic Review in TSCA Risk Evaluations Document* (U.S. EPA, 2018a). Additional details can be found in EPA's *Strategy for Conducting Literature Searches for N-Methylpyrrolidone (NMP): Supplemental File to the TSCA Scope* document (U.S. EPA, 2017e). The results of this screening process are published in the

NMP (CASRN 872-50-4) Bibliography: Supplemental File to the TSCA Scope Document (U.S. EPA, 2017b).

1.5.2 Data Evaluation

During the data evaluation stage, EPA assessed the quality of the data sources using the evaluation strategies and criteria described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). EPA evaluated the quality of all data sources that passed full-text screening. Each data source received an overall confidence rating of high, medium, low or unacceptable.

The results of the data quality evaluations are summarized in Sections 2.1 (Fate and Transport), 2.2 (Releases to the Environment), 2.3 (Environmental Exposures), 2.4 (Human Exposures), 3.1 (Environmental Hazards), and 3.2 (Human Health Hazards). Supplemental files 1A-1H (see list of supplemental files in Appendix B) also provide details of the data evaluations including individual metric scores and the overall study score for each data source.

1.5.3 Data Integration

Data integration includes analysis, synthesis and integration of information for the risk evaluation. During data integration, EPA considers quality, consistency, relevance, coherence and biological plausibility to make final conclusions regarding the weight of the scientific evidence. As stated in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a), data integration involves transparently discussing the significant issues, strengths, and limitations as well as the uncertainties of the reasonably available information and the major points of interpretation (U.S. EPA, 2018d).

EPA used previous assessments to identify key and supporting information and then analyzed and synthesized available lines of evidence regarding NMP's chemical properties, environmental fate and transport properties and its potential for exposure and hazard. EPA's analysis also considered recent data sources that were not considered in the previous assessments (Section 1.5.1) as well as reasonably available information on potentially exposed or susceptible subpopulations.

The exposures and hazards sections describe EPA's analysis of the relevant lines of evidence that were found acceptable for the risk evaluation based on the data quality reviews provided in the supplemental files.

2 EXPOSURES

This section describes EPA's approach to assessing environmental and human exposures. First, the fate and transport of NMP in the environment is characterized. Then, NMP environmental releases are assessed. Last, this information is integrated into an assessment of occupational and consumer exposures (including potentially exposed or susceptible subpopulations). For all exposure-related disciplines, EPA screened, evaluated, extracted and integrated reasonably available empirical data. In addition, EPA used models to estimate exposures. Both empirical data and modeled estimates were considered when selecting values for use in the exposure assessment.

The exposure pathways evaluated in the current assessment include dermal, vapor-through-skin and inhalation. NMP is well absorbed following dermal exposures and dermal absorption including NMP from the vapor phase typically contributes significantly to human exposure (Bader et al., 2008; Keener et al., 2007). NMP diluted in water has reduced dermal absorption (Keener et al., 2007; Payan et al., 2003) while NMP diluted in other solvents, such as d-limonene, can increase the absorption of NMP (Huntingdon Life Sciences, 1998) and prolonged exposures to neat (i.e., pure) NMP increases the permeability of the skin (RIVM, 2013). NMP is also absorbed via inhalation (Akesson and Paulsson, 1997) but the low vapor pressure and mild volatility can limit the amount of NMP available for inhalation. For nearby non-users, exposures were limited to inhalation and vapor-through-skin exposure routes. In all cases, internal doses integrating the different exposure routes were derived using a PBPK model.

The previously published PBPK model for NMP (Poet et al., 2010) was adapted for use by EPA and described in Appendix I. The model predicted absorption of liquid or vapor from the NMP concentration, duration of contact and physiological descriptions such as body weight. The physiological parameters of body weight and skin surface area used were specific to pregnant women and women of childbearing age for acute exposures and to men for chronic exposures. Absorption of NMP via inhalation depended on the NMP concentrations in air. Dermal absorption of NMP depended on the NMP weight fraction in liquid, NMP vapor concentration and skin surface area exposed to liquid and vapor. The thickness of the liquid film did not factor directly into the estimate of liquid NMP absorption. As a conservative estimate for user scenarios it was assumed that fresh material would be constantly deposited over the time of use such that the concentration on the skin would remain essentially constant at the formulation concentration. For example, a thin layer of compound is assumed to cover the surface area of the hands due the activities of the condition use, which may include use of sponges or rags with either both hands or one hand covered for high end and central tendency, respectively. The exposure parameters used to estimate internal NMP doses for the occupational and consumer exposure scenarios are described below.

Exposure equations and selected values used in the exposure assessment are presented in the following sections. More specific information is provided in Supplementary Files.
Following inclusion of NMP on EPA's TSCA Chemical Work Plan list in 2012, EPA published an assessment of the human health risks associated with NMP use in paint and coating removal (U.S. EPA, 2015) prior to passage of the Lautenberg Act amendments to TSCA. Since that time, EPA has published the Scope (U.S. EPA, 2017d) and Problem Formulation (U.S. EPA, 2018c) for the current risk evaluation.

2.1 Fate and Transport

The environmental fate studies considered for this assessment are summarized in Table 2-1. This information has not changed from that provided in the NMP Problem Formulation (U.S. EPA, 2018c).

2.1.1 Fate and Transport Approach and Methodology

Environmental fate data were evaluated using the environmental fate data quality criteria outlined in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). The study evaluation results are documented in the data evaluation tables presented in EPA-HQ-OPPT-2019-0236. Environmental fate data from studies which met data quality requirements (as indicated by high, medium, or low data quality scores) were extracted and integrated into the current risk evaluation to characterize the environmental fate of NMP.

EPA gathered and evaluated environmental fate information according to the process described in the Application of Systematic Review in TSCA Risk Evaluations (U.S. EPA, 2018a). Reasonably available environmental fate data were selected for use in the current evaluation. EPA also used environmental fate and transport characteristics of NMP described in previous regulatory and non-regulatory assessments to inform the environmental fate and transport information discussed in this section and in Appendix C. EPA has high confidence in the information used in the previous assessments to describe the environmental fate and transport of NMP and thus used it to make scoping decisions.

Although EPA conducted a comprehensive literature search and screening process as described in Section 1.5, information reported in previous chemical assessments was also used to identify key and supporting studies that could inform the current analysis (i.e., information supporting key assumptions, arguments, and/or conclusions). Where applicable, EPA also considered newer information that was not considered in the previous chemical assessments. EPA did not critically evaluate all underlying evidence ever published on the environmental fate and transport of NMP, but instead focused its data evaluation efforts on key and supporting studies identified previously, and any relevant information identified subsequently. Using this pragmatic approach, EPA maximized its own resources and the scientific and analytical efforts of other regulatory and non-regulatory agencies by accepting for the most part, the scientific knowledge gathered and analyzed by others. As a result, a smaller pool of information was subjected to the TSCA systematic review process to ensure that the NMP risk evaluation uses the best available science to support the weight of the scientific evidence.

Please note that other data sources may be cited as part of the reasonably available evidence presented on the fate and transport properties of NMP. For instance, EPA assessed the quality of a study on the ready biodegradability of NMP (U.S. EPA, 2019i) based on the data quality criteria described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a) and the study was determined to be of 'medium' confidence. Other fate estimates were based on modeling results from EPI Suite™ (U.S. EPA, 2012c), a predictive tool for physical/chemical and environmental fate properties. The data evaluation tables describing the review of key and supporting fate data sources can be found in the supplemental document,

Systematic Review Supplemental File: Data Quality Evaluation of Environmental Fate and Transport Studies (U.S. EPA, 2019).

The NMP physical-chemical properties and environmental fate characteristics used in the current assessment are presented in Tables 1-1 and 2-1, respectively. EPA used EPI Suite™ estimations and reasonably available fate data to characterize the environmental fate and transport of NMP. During problem formulation, EPA also analyzed the air, water, sediment, land and biosolids pathways. These results are described in the NMP Problem Formulation document (U.S. EPA, 2018c).

Environmental fate data from studies were evaluated using the environmental fate data quality criteria outlined in *The Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). The study evaluation results are documented in Appendix C. Environmental fate data from acceptable studies were extracted and integrated during risk evaluation. Based on the results obtained from the data quality evaluation process EPA has high confidence in the studies used to characterize the environmental fate of NMP. The data extracted from environmental fate studies are shown in Appendix C and the full environmental fate data quality ratings are presented in the supplemental file (U.S. EPA, 2019).

NMP does not persist in the environment. Upon release into the atmosphere, it is degraded via reaction with photo-chemically produced hydroxyl radicals in ambient air. The half-life for this reaction is approximately 5.8 hours, assuming a hydroxyl radical concentration of 1.5 × 106 hydroxyl radicals/cm3 air and a 12-hour day (U.S. EPA, 2015). NMP is hygroscopic and can dissolve in water droplets. Atmospheric releases may be removed by condensation or further reaction with hydroxyl radicals.

Although neat (pure) NMP is slightly volatile, volatilization from water and moist soils is not likely based on its Henry's Law constant (3.2 × 10-9 atm m3/mole). NMP is not expected to adsorb to suspended solids or sediment upon release to water due to its estimated soil organic carbon/water partition coefficient (log Koc = 0.9). NMP exhibits high mobility in soil; hence, environmental releases are expected to migrate from soil to ground water (U.S. EPA, 2012c).

EPI Suite™ (U.S. EPA, 2012c) modules were used to predict volatilization of NMP from wastewater treatment plants, lakes and rivers. The EPI Suite™ module that estimates chemical removal in sewage treatment plants ("STP" module) was run to evaluate the potential for NMP to biodegrade, volatilize to air or adsorb to sludge during wastewater treatment. The STP module, using BIOWIN predictions for biodegradation rates, estimates that most of NMP releases to wastewater (> 90%) will be removed by biodegradation. BIOWIN model predictions further indicate negligible removal of NMP (< 1%) via adsorption to sludge or volatilization to air. The EPI Suite™ input values are listed in Appendix C, Figure_C1 and the EPI Suite™ output are listed in the NMP Fate Supplementary Document (U.S. EPA, 2019).

963 **Table 2-1. Environmental Fate Characteristics of NMP**

Property or Endpoint	Value [a]	Reference	Study Quality
Direct photo-degradation	Not available		
Indirect photo-degradation	5.8 hours (estimated for atmospheric degradation)[b]	(U.S. EPA, 2012c)	High
Hydrolysis half-life	Does not undergo hydrolysis	(U.S. EPA, 2015)	NA
Biodegradation	45% COD/2wks; (95% in 2weeks based on GC peak disappearance) [aerobic in static die-away system test, sewage sludge inoculum, OECD 301A]	(Chow and Ng, 1983)	High (1.37)
	73% in 28 days (aerobic in water, Ready Biodegradability, Modified Ministry of International Trade and Industry (MITI), OECD 301C)	(Toxicology and Regulatory Affairs, 2003)	Medium (1.8)
Bioconcentration factor (BCF)	3.16 (estimated)[b]	(U.S. EPA, 2012c)	High
Bioaccumulation factor (BAF)	0.9 (estimated)[b]	(U.S. EPA, 2012c)	High
Soil organic carbon/water partition coefficient (log K_{oc})	0.9 (estimated)[b]	(U.S. EPA, 2012c)	High

[a] Measured unless otherwise noted.
[b] Information was estimated using EPI Suite (U.S. EPA, 2012c)
NA: Not applicable

964
965 The EPI Suite™ module that estimates volatilization from lakes and rivers was run using default
966 settings to evaluate the potential for NMP to volatilize from surface water. The model results
967 indicate that volatilization from surface water is unlikely to be a significant removal pathway for
968 NMP. Aerobic biodegradation is expected to be the primary removal pathway for NMP in many
969 surface water environments based on measured data (see Table 2-1).
970
971 Experimental data and EPI Suite™ model predictions indicate that NMP will degrade in aerobic
972 environments; however, the BIOWIN module within EPI Suite™ that estimates anaerobic
973 biodegradation potential (BIOWIN 7) (U.S. EPA, 2019i, 2012c) predicts that NMP will not
974 rapidly biodegrade under anaerobic conditions. These model predictions are consistent with
975 previous assessments of NMP degradation potential (OECD, 2007b; Toxicology and Regulatory
976 Affairs, 2003; WHO, 2001; U.S. EPA, 1998; Chow and Ng, 1983).

NMP exhibits low potential for bioaccumulation and bioconcentration in the environment. Measured bioconcentration studies for NMP were not presented in EPA's previous evaluation of risks associated with NMP use in paint and coating removal (U.S. EPA, 2015); however, based on the estimated BAF and BCF values (0.9 and 3.16, respectively), NMP is not expected to bioaccumulate or bioconcentrate in aquatic organisms (U.S. EPA, 2012c; OECD, 2007b; U.S. EPA, 1999).

2.2 Releases to the Environment

Releases to the environment from conditions of use (e.g., industrial and commercial processes, commercial or consumer uses resulting in down-the-drain releases) are one component of potential exposure that may be derived from reported data obtained through direct measurement, calculations based on empirical data and/or model assumptions.

Under the Emergency Planning and Community Right-to-Know Act (EPCRA) Section 313, NMP has been a TRI-reportable substance effective January 1, 1995. The TRI database includes information on disposal and other releases of NMP to air, water, and land, in addition to how it is managed through recycling, treatment, and burning for energy recovery. EPA analyzed the TRI data and examined the definitions of elements in the TRI data to determine the level of confidence that a release would result from specific types of land disposal (i.e., RCRA Subtitle C hazardous landfills and Class I underground injection wells) and incineration. EPA also examined how NMP is treated at industrial facilities. Based on 2015 TRI reporting, an estimated 14,093 lbs of NMP was released to surface water from industrial sources. See Table_Apx D-1 in Appendix D for a TRI summary table and further details on recent releases of NMP to various media.

2.3 Environmental Exposures

NMP may occur in various environmental media including sediment, soil, water and air. As part of the NMP Problem Formulation (U.S. EPA, 2018c), EPA completed a preliminary analysis of environmental exposures for aquatic terrestrial species to NMP in these environmental media. No additional information has been received or otherwise identified by EPA that would alter the conclusions presented in the NMP Problem Formulation (U.S. EPA, 2018c). EPA concluded that no further analysis of environmental release pathways for environmental receptors is necessary based on a qualitative assessment of the physical chemistry and fate properties of NMP and the levels of NMP exposure that may be expected for organisms that inhabit these environmental compartments.

The evaluation of environmental exposures from the NMP Problem Formulation (U.S. EPA, 2018c) is summarized in the following subsections on potential presence in biological tissues (biota), and possible exposures for aquatic and terrestrial receptors. The information is provided for clarity in this RE and the conclusions remain unchanged from the NMP Problem Formulation (U.S. EPA, 2018c).

2.3.1 Presence in the Environment and Biota

NMP exhibits low potential for bioaccumulation and bioconcentration in the environment. Based on the estimated BAF and BCF values (0.9 and 3.16, respectively) (see Table 2-1), NMP

is not expected to bioaccumulate or bioconcentrate in aquatic organisms (U.S. EPA, 2012c; OECD, 2007b; U.S. EPA, 1999).

2.3.2 Aquatic Environmental Exposures

EPA used data from EPA's Toxics Release Inventory (TRI) and EPA's Exposure and Fate Assessment Screening Tool, Version 2014 (E-FAST 2014;) to estimate the concentrations of NMP released to surface water near discharging facilities. This exposure assessment for NMP is considered a screening level analyses as it estimates conservative (higher end) surface water concentrations. The assessment was conducted using data for the top 12 releasers reporting to the TRI. Surface water concentrations were estimated based on the 2015 TRI data and EPA's E-E-FAST, Version 2014 (E-FAST 2014). This exposure analysis is included in Appendix D of this RE and is also the same as that performed in the NMP Problem Formulation (U.S. EPA, 2018c). Using the 2015 TRI data and EPA's first-tier, Probabilistic Dilution Model (PDM) within E-FAST, facilities reporting the largest releases of NMP, surface water concentrations of NMP were modeled based on the assumption of 12 or 250 days of release. The 12-day release scenario represents an acute exposure scenario (wherein periodic maintenance and cleaning activities could result in monthly releases). The 250-day release scenario represents a chronic exposure scenario (wherein standard operations may result in continuous discharges of NMP) (see Appendix D). The "high-end" surface water concentrations (i.e., obtained assuming a low stream flow for the receiving water body) ranged from 224 µg/L for the maximum acute scenario (fewer than 20 days of environmental releases per year) to 1,496 µg/L for the maximum chronic exposure scenario (more than 20 days of environmental releases per year), respectively. These predicted acute and surface water concentrations are compared to the Concentrations of Concern identified for aquatic organisms in Section 3.1 for Environmental Hazards (Effects) to estimate Environmental Risk in Section 4.1.

2.4 Human Exposures

EPA evaluated acute and chronic exposures to workers and occupational non-users and acute exposures to consumers by dermal contact with liquids, vapor-through-skin, and inhalation routes in association with NMP use in industrial, commercial, and consumer applications. EPA assessed these exposures by inputting exposure parameters into a physiologically based pharmacokinetic (PBPK) model, which is described in Appendix I.

The conditions of use to be assessed were described in Table 1-6. Due to expected similarities in or the lack of data to distinguish between exposure scenarios for different conditions of use, occupational exposures or consumer exposures for several of the subcategories of use in Table 1-6 were grouped and assessed together during risk evaluation. For example, formulation of paints, coatings, adhesives and sealants may generally have similar worker activities, and EPA does not have data to distinguish whether workers are differently exposed for these different formulations. Therefore, EPA has grouped these formulating conditions of use into one occupational exposure scenario group (Incorporation into Formulation, Mixture, or Reaction Product). Occupational groupings and consumer groupings are assessed separately. A crosswalk of the conditions of use listed in Table 1-6 with the occupational and consumer exposure scenarios assessed in this report is provided in Table 2-2. EPA assessed 26 occupational and consumer exposure scenarios and applied them to 52 conditions of use.

1063 **Table 2-2. Crosswalk of Conditions of Use to Occupational and Consumer Scenarios**
1064 **Assessed in the Risk Evaluation**

Life Cycle Stage	Category [a]	Subcategory [b]	Occupational Exposure Scenario	Consumer Exposure Scenario
Manufacture	Domestic Manufacture	Domestic Manufacture	Section 2.4.1.2.1 - Manufacturing	N/A
	Import	Import	Section 2.4.1.2.2 - Repackaging	N/A
Processing	Processing as a reactant or intermediate	Intermediate in Plastic Material and Resin Manufacturing and in Pharmaceutical and Medicine Manufacturing	Section 2.4.1.2.3 - Chemical Processing, Excluding Formulation	N/A
		Other		
	Incorporated into formulation, mixture or reaction product	Adhesives and sealant chemicals in Adhesive Manufacturing	Section 2.4.1.2.4 - Incorporation into Formulation, Mixture, or Reaction Product	N/A
		Anti-adhesive agents in Printing and Related Support Activities		
		Paint additives and coating additives not described by other codes in Paint and Coating Manufacturing; and Print Ink Manufacturing		
		Processing aids not otherwise listed in Plastic Material and Resin Manufacturing		

		Manufacturing; Primary Metal Manufacturing; Soap, Cleaning Compound and Toilet Preparation Manufacturing; Transportation Equipment Manufacturing; All Other Chemical Product and Preparation Manufacturing; Printing and Related Support Activities; Services; Wholesale and Retail Trade		
		Surface active agents in Soap, Cleaning Compound and Toilet Preparation Manufacturing		
Processing	Incorporated into formulation, mixture or reaction product	Plating agents and surface treating agents in Fabricated Metal Product Manufacturing	Section 2.4.1.2.4 - Incorporation into Formulation, Mixture, or Reaction Product	N/A
		Solvents (which become part of product formulation or mixture) in Electrical Equipment, Appliance and Component Manufacturing; Other Manufacturing; Paint and Coating Manufacturing; Print Ink Manufacturing; Soap, Cleaning Compound and Toilet Preparation Manufacturing; Transportation Equipment Manufacturing; All Other Chemical Product and Preparation Manufacturing; Printing and Related Support Activities; Wholesale and Retail Trade		
		Other uses in Oil and Gas Drilling, Extraction and Support Activities; Plastic Material and Resin Manufacturing; Services		

	Incorporated into article	Lubricants and lubricant additives in Machinery Manufacturing	Section 2.4.1.2.5 - Metal Finishing	N/A
		Paint additives and coating additives not described by other codes in Transportation Equipment Manufacturing	Section 2.4.1.2.5 - Application of Paints, Coatings, Adhesives, and Sealants	N/A
		Solvents (which become part of product formulation or mixture), including in Textiles, Apparel and Leather Manufacturing	Section 2.4.1.2.4 - Incorporation into Formulation, Mixture, or Reaction Product	N/A
Processing	Incorporated into article	Other, including in Plastic Product Manufacturing	Section 2.4.1.2.3 - Chemical Processing, Excluding Formulation	N/A
	Recycling	Recycling	Section 2.4.1.2.16 - Recycling and Disposal	N/A
	Repackaging	Wholesale and Retail Trade	Section 2.4.1.2.2 - Repackaging	N/A
Distribution in commerce	Distribution	Distribution in commerce	Activities related to distribution (e.g., loading, unloading) are considered throughout the life cycle rather than using a single distribution scenario, so are not separately assessed.	N/A
Industrial, commercial, and consumer use	Paints and coatings	Paint and coating removers	Section 2.4.1.2.6 - Removal of Paints, Coatings, Adhesives, and Sealants	Section 2.4.2 - Paint Removers
		Adhesive removers		Section 2.4.2 - Adhesive Removers

		Lacquers, stains, varnishes, primers and floor finishes	Section 2.4.1.2.7 - Application of Paints, Coatings, Adhesives, and Sealants	Section 2.4.2 - Stains, Varnishes
		Powder coatings (surface preparation)		N/A
	Paint additives and coating additives not described by other codes	Use in Computer and Electronic Product Manufacturing, Construction, Fabricated Metal Product Manufacturing, Machinery Manufacturing, Other Manufacturing, Paint and Coating Manufacturing, Primary Metal Manufacturing, Transportation Equipment Manufacturing, Wholesale and Retail Trade		Section 2.4.2 - Paint
				Section 2.4.2 - Arts and Crafts
	Solvents (for cleaning or degreasing)	Use in Electrical Equipment, Appliance and Component Manufacturing.	Section 2.4.1.2.8 – Electronic Parts Manufacturing	N/A
	Ink, toner, and colorant products	Printer ink	Section 2.4.1.2.9 - Printing and Writing	N/A
		Inks in writing equipment		N/A
	Processing aids, specific to petroleum production	Petrochemical Manufacturing	Section 2.4.1.2.3 - Chemical Processing, Excluding Formulation	N/A
Industrial, commercial, and consumer use	Adhesives and sealants	Adhesives and sealant chemicals including binding agents	Section 2.4.1.2.5 - Application of Paints, Coatings, Adhesives, and Sealants	N/A
		Single component glues and adhesives, including lubricant adhesives		Section 2.4.2 - Adhesives
		Two-component glues and adhesives, including some resins		Section 2.4.2 - Sealants
		Soldering materials	Section 2.4.1.2.10 - Soldering	N/A

	Other uses	Anti-freeze and de-icing products	Section 2.4.1.2.11 - Commercial Automotive Serving	N/A
		Automotive care products		Section 2.4.2 - Auto Interior Cleaner Auto Interior Spray Cleaner
		Lubricants and greases		N/A
		Metal products not covered elsewhere	Section 2.4.1.2.5 - Metal Finishing	N/A
		Laboratory chemicals	Section 2.4.1.2.12 - Laboratory Use	N/A
		Lithium ion batteries [c]	N/A	N/A
		Cleaning and furniture care products, including wood cleaners, gasket removers	Section 2.4.1.2.13 - Cleaning	Section 2.4.2 - Cleaners/ Degreasers Engine Cleaner/ Degreaser
		Other uses in Oil and Gas Drilling, Extraction and Support Activities	Section 2.4.1.2.3 - Chemical Processing, Excluding Formulation	N/A
		Lubricant and lubricant additives, including hydrophilic coatings	Section 2.4.1.2.5 - Metal Finishing	Section 2.4.2 - Spray Lubricant
		Fertilizer and other agricultural chemical manufacturing - processing aids and solvents	Section 2.4.1.2.14 - Fertilizer Application	N/A
		Pharmaceutical and Medicine Manufacturing - functional fluids (closed systems)	Section 2.4.1.2.3 - Chemical Processing, Excluding Formulation	N/A

		Wood preservatives	Section 2.4.1.2.15 - Wood Preservatives	N/A
Disposal	Disposal	Industrial pre-treatment	Section 2.4.1.2.16 - Recycling and Disposal	N/A
		Industrial wastewater treatment		N/A
		Publicly owned treatment works (POTW)		N/A
		Underground injection		N/A
		Landfill (municipal, hazardous or other land disposal)		N/A
		Incinerators (municipal and hazardous waste)		N/A
		Emissions to air		N/A

[a] These categories of conditions of use appear in the Life Cycle Diagram, reflect CDR codes, and broadly represent conditions of use of NMP in industrial and/or commercial settings.
[b] These subcategories reflect more specific uses of NMP
[c] This condition of use applies to manufacture and processing.
N/A means these conditions of use are not applicable to occupational or consumer exposures

1065

2.4.1 Occupational Exposures

For the purpose of this assessment, EPA considered occupational exposure of the total workforce of exposed users and non-users, which include but are not limited to male and female workers of reproductive age who are >16 years of age. Female workers of reproductive age are >16 to less than 50 years old. Adolescents (>16 to <21 years old) are a small part of this total workforce. The occupational exposure assessment is applicable to and covers the entire workforce who are exposed to NMP.

EPA evaluated acute and chronic exposures to workers and occupational non-users (ONUs) associated with dermal contact with liquids (workers only), vapor-through-skin, and inhalation routes in association with NMP use in industrial and commercial applications, which are shown in Table 2-2. Oral exposure via incidental ingestion of inhaled vapor/mist/dust will be considered as an inhalation exposure as noted in Figure 1-2 because EPA does not have data or methods to fractionate the total NMP inhaled into the amount of NMP that deposits in the upper respiratory system and the amount of NMP that goes into the lung.

EPA assessed these exposures by inputting exposure parameters into a physiologically based pharmacokinetic (PBPK) model, which is described in Appendix I. Parameter development for each occupational exposure scenario assessed is described in Section 2.4.1.1. More detailed information about the parameter development may be found in the supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r).

For each scenario, EPA distinguishes between exposures to workers and ONUs when possible. A primary difference between workers and ONUs is that workers may have direct dermal contact with liquid chemicals that they handle, whereas ONUs located in the general vicinity of workers do not have direct dermal contact with liquids handled by the workers. Examples of ONUs include supervisors, managers, and other employees that may be in the production areas but do not perform tasks that result in direct dermal contact with liquids. EPA expects that ONUs are exposed to lower air concentrations than workers since they may be further from the emission source than workers. When EPA cannot distinguish ONU exposures from workers, EPA assumes ONUs are exposed to lower air concentrations as compared to workers.

2.4.1.1 Occupational Exposures Approach and Methodology

This section summarizes the occupational dermal and inhalation exposure parameters and concentrations for NMP in the various industries and scenarios shown in Table 2-2. These parameters were used as PBPK model inputs for the risk evaluation. The supplemental document, *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r) provides background details on industries that may use NMP, worker activities, processes, numbers of sites and numbers of potentially exposed workers. This supplemental document also provides detailed discussion on the values used for the dermal exposure parameters and air concentrations and associated worker inhalation parameters presented in this section.

Key Parameters for PBPK Modeling

To derive internal exposure estimates for acute and chronic occupational exposures, the PBPK model required a set of input parameters related to exposures by the dermal and inhalation routes:

- NMP weight fraction in the liquid product;
- Total skin surface area of hands in contact with the liquid product;
- Glove protection factor (if applicable);
- Duration of dermal contact with the liquid product;
- Air concentration for inhalation and vapor-through-skin exposure; and
- Body weight of the exposed worker.

EPA assumed that the skin of the hands was exposed dermally to NMP at the specified liquid weight fraction and skin surface area and that there was simultaneous exposure by inhalation and vapor-through-skin absorption for unobstructed skin areas. As described below, air concentrations were adjusted to duration of contact of liquid on the skin, which is assumed to be removed by cleaning at the end of the work period. Acute scenarios assumed 1 day of exposure and chronic scenarios assumed 5 days of exposure per week.

EPA used literature sources for estimating many of these occupational exposure parameters. EPA used modeling or generic assumptions when data were not available.

For most PBPK input parameters, EPA did not find enough data to determine statistical distributions of the actual exposure parameters and concentrations. Within the distributions, central tendencies describe 50th percentile or the substitute that most closely represents the 50th percentile. The high-end of a distribution describes the range of the distribution above 90th percentile (U.S. EPA, 1992). Ideally, EPA would use the 50th and 95th percentiles for each parameter. Where these statistics were unknown, the mean or mid-range (mean is preferable to mid-range) served as substitutes for 50th percentile and the high-end of ranges served as a substitute for 95th percentile. However, these substitutes were uncertain and not ideal substitutes for the percentiles. EPA could not determine whether these substitutes were suitable to represent statistical distributions of real-world scenarios.

EPA selected grouped sets of individual input parameter values intended to represent central tendency and high-end occupational exposure scenarios. To generate each central tendency scenario result, EPA used a group of all central tendency input parameter values relevant to the scenario. To generate each high-end scenario result, EPA used a group of mostly high-end input parameter values relevant to the scenario except body weight, which is a median value. Using mostly high-end input values is a plausible approach to estimate a high-end PBPK result for the periods of acute and chronic exposures of 1 to 5 days.

Weight Fraction

To support this risk evaluation, EPA determined the weight fraction of NMP in various products through information provided in the available literature, previous risk assessments and the 2017 NMP Market Profile (Abt, 2017). This Market Profile was prepared in part by searching Safety Data Sheets (SDSs) of products that contain NMP and compiling the associated name, use, vendor and NMP concentration associated with each of these products. Where a data point was provided as range of NMP concentrations for a certain product (e.g., paints and coatings), EPA utilized the mid-range (middle) and high-end (maximum) weight fractions to estimate potential exposures. Where multiple data points for a given type of product (e.g., paints and coatings) were available, EPA estimated exposures using the central tendency (50th percentile) and high-end (95th percentile) NMP concentrations.

Skin Surface Area

For both consumer and occupational user dermal exposure for liquid contact, EPA used skin surface area values both for the hands of females and for the hands of males, obtained from the 2011 edition of EPA's Exposure Factors Handbook (Table 7-13) (U.S. EPA, 2011). These values overestimate exposures for younger members of the workforce whose hand surface areas would be smaller. One exception is for the OES that includes Writing, 1 cm^2 was assumed based on a literature estimate for writing inks (NICNAS, 2016). For the remainder of the occupational dermal exposure assessment, EPA used the following values:

- high-end value, which represents two full hands in contact with a liquid: 890 cm^2 (female),1070 cm^2 (males)
- central tendency value, which is half of two full hands (equivalent to one full hand) in contact with a liquid and represents only the palm-side of both hands exposed to a liquid: 445 cm^2 (females), 535 (males)

Occupational non-users (ONUs) are not expected to have direct contact with NMP-based liquid products unless an incident (e.g., spill) were to occur. However, PBPK modeling of ONU (no liquid contact) used a skin surface area value of 0.1 cm^2 (about 0.1% of values used for occupational users) for liquid exposure to prevent a division by zero error in model equations.

For dermal exposure to vapor for both occupational users and ONUs, the PBPK modeled up to 25% of the total skin surface area, corresponding to the face, neck, arms and hands, as exposed to and capable of absorbing vapors, minus any area covered by personal protection equipment (PPE). This area, which is programmed into the PBPK model, is not a variable input value.

Glove Usage

EPA also made assumptions about glove use and associated protection factors (PFs). Where workers wear gloves, workers are exposed to NMP-based product that penetrates the gloves, including potential seepage through the cuff from improper donning of the gloves, permeation of NMP through the glove material, and the gloves may occlude the evaporation of NMP from the skin. Where workers do not wear gloves, workers are exposed through direct contact with NMP.

Overall, EPA understands that workers may potentially wear gloves but does not know the likelihood that workers wear gloves of the proper type and have training on the proper usage of gloves. Some sources indicate that workers wear chemical-resistant gloves (Meier et al., 2013; OECD, 2009a; NICNAS, 2001), while others indicate that workers likely wear gloves that are more permeable than chemical-resistant gloves (RIVM, 2013). No information on employee training was found. Data on the prevalence of glove use is not available for most uses of NMP. One anecdotal survey of glove usage among workers performing graffiti removal indicates that 87% of workers wear gloves, although the glove materials varied and were sometimes not protective; only a small fraction of these workers used gloves made of optimal material for protection against NMP and some used cloth or leather gloves (Anundi et al., 2000). Prior to the initiation of this risk evaluation EPA had gathered information in support of understanding glove use for handling pure NMP and for paint and coatings removal using NMP formulations. This information may be generally useful for a broader range of uses of NMP and is presented for illustrative purposes in 6E.1.1. SDSs found by EPA recommend glove use (see Appendix E.1.2). Initial literature review suggests that there is unlikely to be enough data to justify a specific probability distribution for effective glove use for a chemical or industry. Instead, the impact of effective

glove use is explored by considering different protection factors, which are further discussed below and compiled in Table 2-3.

Gloves only offer barrier protection until the chemical breaks through the glove material. Using a conceptual model, Cherrie et al. (2004) proposed a glove workplace PF – the ratio of estimated uptake through the hands without gloves to the estimated uptake through the hands while wearing gloves: this protection factor is driven by glove usage practices and by flux, which varies with time. The ECETOC TRA v3 model represents the protection factor of gloves as a fixed, assigned protection factor equal to 1, 5, 10, or 20 (Marquart et al., 2017). When assuming glove use, EPA assumed protection factors using this strategy. Given the limited state of knowledge about the protection afforded by gloves in the workplace, it is reasonable to utilize the PF values of the ECETOC TRA v3 model (Marquart et al., 2017), rather than attempt to derive new values.

For each occupational exposure scenario, EPA used professional judgment to predict the likelihood of the use of gloves based on the characteristics described in Table 2-3, and the associated PFs are presented as what-if scenarios. For OESs with only industrial sites, EPA assumes that workers are likely to wear protective gloves and have basic training on the proper usage of these gloves, corresponding to a protection factor of 10 for both the central tendency and high-end exposure scenarios. In high-end scenarios that include both commercial and industrial sites, EPA assumes that either no gloves are used or, if gloves are used, that glove material may not be protective, each of which corresponds to a protection factor of 1. This assumption is based on the survey of graffiti removers noted that only a small fraction of these workers used gloves made of optimal material for protection against NMP and some used cloth or leather gloves (Anundi et al., 2000). For these same scenarios, EPA assesses a central tendency scenario assuming the use of gloves with minimal to no employee training, corresponding to a protection factor of 5. As indicated in Table 2-3, use of protection factors above 1 is valid only for glove materials that have been tested for permeation against the NMP-containing liquids associated with the condition of use. EPA has not found information that would indicate specific activity training (e.g., procedure for glove removal and disposal) for tasks where dermal exposure can be expected to occur in a majority of sites in industrial only OESs, so the PF of 20 is not assumed for any central tendency or high-end estimates but would be applicable to lower percentile (below central tendency) exposure estimates. Additional explanations of the selection of PFs for each exposure scenario and of occlusion are included in the supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r).

In addition to the assumed central tendency and high-end scenarios, EPA conducted additional modeling of exposures for the full range of glove use or no glove use to determine impacts on exposures and MOEs as what-if scenarios. The results of this additional modeling are shown in Section 4.2.2.

Table 2-3. Glove Protection Factors for Different Dermal Protection Strategies from ECETOC TRA v3

Dermal Protection Characteristics	Setting	Protection Factor, PF
a. No gloves used, or any glove / gauntlet without permeation data and without employee training	Industrial and Commercial Uses	1
b. Gloves with available permeation data indicating that the material of construction offers good protection for the substance		5
c. Chemically resistant gloves (i.e., as *b* above) with "basic" employee training		10
d. Chemically resistant gloves in combination with specific activity training (e.g., procedure for glove removal and disposal) for tasks where dermal exposure can be expected to occur	Industrial Uses Only	20

Duration of Dermal Contact

Where available, EPA utilized exposure durations from the available task-based inhalation monitoring data. No dermal duration data were found. In lieu of dermal duration data or task-based durations from inhalation monitoring data, EPA assumed a minimum duration of 1 hour/day, which is a reasonable assumption considering the initial contact time with the formulation containing NMP plus the time after direct contact when the thin film evaporates from and absorbs into the skin. EPA assumed a high-end value of 8 hours/day (i.e., a full shift). As a central tendency estimate, EPA assumed a mid-range value of 4 hours/day (the calculated mid-point of 4.5 was rounded to 4 hours/day). The low-end and high-end values are consistent with EPA's documented standard model assumptions for occupational dermal exposure modeling (U.S. EPA, 1991a).

Air Concentration for Inhalation and Vapor-through-Skin Exposure

EPA reviewed workplace inhalation monitoring data collected by government agencies such as OSHA and NIOSH, and monitoring data found in published literature (i.e., personal exposure monitoring data and area monitoring data). Data were evaluated using the evaluation strategies laid out in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a), and the evaluation details are shown in two supplemental files: *Risk Evaluation for N-Methylpyrrolidone (NMP), Systematic Review Supplemental File: Data Quality Evaluation for Occupational Exposure and Release Data* (U.S. EPA, 2019p) and *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) Systematic Review Supplemental File: Data Quality Evaluation of Environmental Releases and Occupational Exposure Common Sources* (U.S. EPA, 2019o). Where available, EPA used air concentration data and estimates found in government or published literature sources to serve as inputs to the PBPK modeling for occupational exposures to NMP. There is not a known correlation between weight fraction of NMP in the material being handled / used and the concentration of NMP in air. Where air concentration data were not available, modeling estimates were used. Details on which models EPA used are included in Section 2.4.1.2 for the applicable OESs and discussion of the uncertainties associated with these models is included in Section 2.4.1.4.

EPA evaluated personal monitoring data or modeled near-field exposure concentrations potential inhalation and vapor-through-skin exposures for workers. Since ONUs do not directly handle NMP,

EPA reviewed personal monitoring data, modeled far-field exposure concentrations, and area monitoring data in evaluating potential inhalation and vapor-through-skin exposures for ONUs. Because modeled results are typically intended to capture exposures in the near-field, modeling that does not contain a specific far-field component are not considered to be suitable for ONUs. Area monitoring data may potentially represent ONU exposures depending on the monitor placement and the intended sample population. Inhalation data sources did not usually indicate whether NMP exposure concentrations were for occupational users or occupational non-users (ONUs). For inhalation and vapor-through-skin exposures, if EPA cannot distinguish ONU exposures from workers, EPA assumes that ONUs experience lower air concentrations compared to workers.

For PBPK modeling, the duration of inhalation exposure must equal the duration of dermal exposure. Therefore, where EPA did not have exposure durations from task-based monitoring data, EPA adjusted air concentrations by multiplying by a ratio of duration of the air concentration averaging time to duration of dermal exposure to liquid, which is discussed above.

Few literature sources indicate the use of respirators for reducing worker exposures to NMP by inhalation. Therefore, EPA central tendency and high-end scenarios do not incorporate protection factors for respirator use. Regarding respirator use, only one of the NMP studies containing worker inhalation data specified the type of respirator used by the workers in the study. This respirator, a half mask air-purifying respirator with organic vapor cartridges (Kiefer, 1994), is classified as having an assigned protection factor (APF) of 10. Therefore, EPA conducted additional modeling representing scenarios below central tendency for the use of respirators providing an APF of 10. This modeling reduces inhalation concentrations by a factor of 10 as intended when this type of respirator is used in accordance with OSHA's Respiratory Protection standard (29 CFR 1910.134). While respirators with other APFs may be used, EPA only included this APF in additional modeling. The results of this additional modeling are shown in Section 4.2.2.

Body Weight

Both the consumer and occupational dermal exposure assessments used the 50th percentile body weights for pregnant women in their first trimester, which is 74 kg, and for males, which is 88 kg, for both central tendency and high-end exposure scenarios. EPA obtained these values from the 2011 edition of EPA's Exposure Factors Handbook (Table 8-29) (U.S. EPA, 2011).

2.4.1.2 Occupational Exposure Scenarios

Details of the data, modeling, and associated exposure-related information for each of the Occupational Exposure Scenarios (OES) listed in Table 2-2 and in the subsections below are available in the supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment*. (U.S. EPA, 2019r)

The following subsections contain a summary of dermal and inhalation parameter estimates for each OES. Information on the number of potentially exposed workers and occupational non-users (ONUs) can be found in Table 2-4. Details on the parameter estimates as well as process descriptions, numbers of sites and potentially exposed workers, and worker activities for each OES are available in the supplemental document (U.S. EPA, 2019r). A summary set of all central tendency and high-end scenarios parameter inputs to the PBPK model is shown in Table 2-66.

Key uncertainties toward exposure estimates are summarized in Section 2.4.1.4.

EPA estimated numbers of workers in the assessed industries. Where available, EPA used CDR data to provide a basis to estimate the numbers of sites, workers, and occupational non-users (ONUs). EPA supplemented the available CDR data with U.S. economic data using the following method:

1. Identify the North American Industry Classification System (NAICS) codes for the industry sectors associated with these uses.
2. Estimate total employment by industry/occupation combination using the Bureau of Labor Statistics' (BLS) Occupational Employment Statistics (OES) data (U.S. BLS, 2016).
3. Refine the OES estimates where they are not sufficiently granular by using the U.S. Census' Statistics of US Businesses (SUSB) (citation) data on total employment by 6-digit NAICS.
4. Use market penetration data to estimate the percentage of employees likely to be using NMP instead of other chemicals.
5. Combine the data generated in Steps 1 through 4 to produce an estimate of the number of employees using NMP in each industry/occupation combination, and sum these to arrive at a total estimate of the number of employees with exposure.

Market penetration data for NMP are not readily available at this time; therefore, site, worker, and ONU estimates do not take this into account and likely overestimate the number of sites, workers, and ONUs potentially exposed to NMP. Where end-use sector is not clear, relevant GSs and ESDs are used to estimate the number of sites and workers, such as for metal finishing.

Estimated numbers of occupational workers in the assessed industries are shown in Table **2-4**. The number of workers exposed to NMP for these industries is not known. Additionally, the proportion of workers that are exposed in an industrial versus commercial setting is unknown. Details of these estimates may be found in the supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r).

Table 2-4. Estimated Numbers of Workers in the Assessed Industry Uses of NMP [a]

Occupational Exposure Scenario	Number of Workers [b]
Manufacturing	2,800 [c]
Repackaging	1,100 [c]
Chemical Processing, Excluding Formulation	5,400 [c]
Incorporation into Formulation, Mixture, or Reaction Product	1,900 [c]
Application of Paints, Coatings, Adhesives and Sealants	2,000,000
Printing and Writing	53,000
Metal Finishing	530,000
Removal of Paints, Coatings, Adhesives and Sealants	410,000
Cleaning	190,000

Commercial Automotive Servicing	910,000
Laboratory Use	420,000
Electronic Parts Manufacturing	660,000
Soldering	4,000,000
Fertilizer Application	1,300,000
Wood Preservatives	380,000
Recycling and Disposal	200 [c]

[a] The number of worker estimates are based on industry-specific data that are independent of NMP usage and the portion of workers that are exposed to NMP within these industries is unknown.
[b] These numbers are rounded to two significant figures.
[c] The number of sites associated with these occupational exposure scenarios were determined from CDR or TRI data. However, the number of workers that are exposed to NMP at these sites is unknown.

2.4.1.2.1 Manufacturing

For this industrial exposure scenario, EPA assessed inhalation, vapor-through-skin, and dermal exposures from the loading of various containers (i.e., drums, tank trucks, rail cars) with pure NMP. While EPA does expect that workers may perform additional activities during this scenario, such as sampling or maintenance work, EPA expects that loading activities present the largest range of potential exposures.

Inhalation and Vapor-through-Skin

EPA found no monitoring data specific to the manufacture of NMP. However, there is a German source with monitoring data for the storing and conveying of pure NMP, which may occur during manufacturing (IFA, 2010). These data do not include additional details such as the industry, associated worker activities, type of storing and conveying systems, and sampling time, resulting in a data quality rating of medium. EPA modeling estimates had higher quality rating, so EPA did not use this German monitoring data. EPA also found a source of European modeling estimates for the manufacturing of NMP (RIVM, 2013). This modeled data had a medium data quality rating and EPA modeling estimates had higher data quality, so EPA did not use the European modeling data. Due to limited relevance and quality of German monitoring data and European modeling estimates found in the published literature, EPA used modeling estimates of air concentrations with the highest data quality for this use. EPA's modeled exposure concentrations are similar in value and the same order of magnitude as the European modeling estimates. EPA's *Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model* involves deterministic modeling and the *Drum Loading and Unloading Release, and Inhalation Exposure Model* involves probabilistic modeling.

The inhalation exposure concentrations modeled by EPA for loading of NMP are summarized into the input parameters used for the PBPK modeling in Table 2-5. Note that the exposure duration for the central tendency and high-end exposure scenarios for loading into drums are the same because the unloading rate does not vary in that model. The supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r) provides additional details.

Table 2-5. Summary of Parameters for PBPK Modeling of Worker Inhalation Exposure During Manufacturing

Work Activity	Parameter Characterization	Full-Shift NMP Air Concentration (mg/m^3, 8-hr TWA)	Duration-Based NMP Air Concentration (mg/m^3)	Source	Data Quality Rating
Loading NMP into bulk containers	Central tendency (50th percentile)	0.047	0.760 (duration = 0.5 hr)	*Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model* (U.S. EPA, 2013a)	Not applicable[a]
	High-end (95th percentile)	0.190	1.52 (duration = 1 hr)		
Loading NMP into drums	Central tendency (50th percentile)	0.427	1.65 (duration = 2.06 hr)	*Drum Loading and Unloading Release and Inhalation Exposure Model* (U.S. EPA, 2013a)	
	High-end (95th percentile)	1.51	5.85 (duration = 2.06 hr)		

[a] - EPA models are standard sources used by EPA for occupational exposure assessments. EPA did not systematically review models that were developed by EPA.

Dermal

Table 2-6 summarizes the parameters used to assess dermal exposure during the manufacturing of NMP. For this life cycle stage, EPA assessed dermal exposures during the loading of pure NMP into bulk containers and into drums. Most of these parameters were determined based on assumptions described in Section 2.4.1.1. EPA used data from 2016 CDR and literature sources to determine the NMP weight fraction. These underlying data have data quality ratings of high. Because this scenario has only industrial sites, EPA assumes that workers are likely to wear protective gloves and have basic training on the proper usage of these gloves for both central and high-end exposures, corresponding to a protection factor of 10.

Table 2-6. Summary of Parameters for Worker Dermal Exposure to Liquids During Manufacturing

Work Activity	Parameter Characterization	Glove Protection Factor(s)	NMP Weight Fraction	Skin Surface Area Exposed [a]	Exposure Duration	Body Weight [a]
			Unitless	cm^2	hr/day	kg
Loading NMP into bulk containers	Central Tendency	10	1	445 (f) 535 (m)	0.5	74 (f) 88 (m)
	High-end	10	1	890 (f) 1,070 (m)	1	
Loading NMP into drums	Central Tendency	10	1	445 (f) 535 (m)	2.06	74 (f) 88 (m)
	High-end	10	1	890 (f) 1,070 (m)	2.06	

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

PBPK Inputs

EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-7.

The numeric parameters corresponding to the characterizations presented in Table 2-7 are summarized in Table 2-8. These are the inputs used in the PBPK model.

Table 2-7. Characterization of PBPK Model Input Parameters for Manufacturing of NMP

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	Loading of bulk containers	Central tendency (50^{th} percentile)	Duration calculated by model	1-hand	Yes	N/A - 100% is assumed for both exposure scenarios
High-end	Loading of drums	High-end (95^{th} percentile)	Duration calculated by model	2-hand	Yes	N/A - 100% is assumed for both exposure scenarios

Table 2-8. PBPK Model Input Parameters for Manufacturing of NMP

Skin Surface Area Exposed (cm^2) [b]Scenario	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Central Tendency	0.760	0.5	445 (f) 535 (m)	10	1	74 (f) 88 (m)
High-end	5.85	2.06	890 (f) 1,070 (m)	10	1	74 (f) 88 (m)

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed to liquid NMP of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Summary

In summary, dermal and inhalation exposures are expected for this use. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

EPA assessed dermal exposure to liquids using the most recent CDR data for concentration provided by industry submitters. Modeling, in the middle of the approach hierarchy, was used to estimate occupational air concentrations for both the loading of NMP into bulk containers and into drums. For modeling of these air concentrations, EPA attempted to address variability in input parameters by estimating both central tendency and high-end parameter values. Additionally, for modeling of air concentrations during the loading of drums, EPA used Monte Carlo simulation to capture variability in input parameters. EPA expects the duration of inhalation and dermal exposure to be realistic for the loading activities, as the durations are based on the length of time to load NMP into specific container sizes (i.e., tank trucks, rail cars, and drums).

Primary Limitations

Due to lack of data, EPA has no method to determine the representativeness of the estimates of duration of inhalation and dermal exposure for the loading activities toward the true distribution for all worker activities. NMP concentration is reported to CDR as a range and EPA assessed only the upper end of the range since a central value cannot be ascertained for this scenario. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage is likely based on professional judgment. The assumed glove protection factor values are uncertain. EPA is uncertain of the accuracy of the emission factors used to estimate fugitive NMP emissions and thereby to model NMP air concentrations. The representativeness of the modeling results toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence
Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium.

2.4.1.2.2 Repackaging

For this industrial exposure scenario, EPA assessed inhalation, vapor-through-skin, and dermal exposures from the unloading of various containers (i.e., drums, tank trucks, rail cars) containing pure NMP. While EPA does expect that workers may perform additional activities during this scenario, such as sampling or maintenance work, EPA expects that unloading activities present the largest range of potential exposures.

Inhalation and Vapor-through-Skin
Since no monitoring data or modeling estimates were found for Repackaging, EPA determined the same monitoring data and modeled exposure estimates for manufacturing could be applied to this occupational exposure scenario, due to the similarity in work activities (e.g., loading vessels) and corresponding NMP concentrations between the two occupational exposure scenarios. The air concentration estimates from Section 2.4.1.2.1 for manufacturing are used for this occupational exposure scenario.

Dermal
EPA compiled the same dermal exposure parameters for this occupational exposure scenario as for manufacturing. The dermal exposure parameters from Section 2.4.1.2.1 for manufacturing are used for this occupational exposure scenario.

PBPK Inputs
EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-9.

The numeric parameters corresponding to the characterizations presented in Table 2-9 are summarized in Table 2-10. These are the inputs used in the PBPK model.

Table 2-9. Characterization of PBPK Model Input Parameters for Repackaging

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	Unloading bulk containers	Central tendency (50th percentile)	Duration calculated by model	1-hand	Yes	N/A - 100% is assumed for both exposure scenarios
High-end	Unloading drums	High-end (95th percentile)	Duration calculated by model	2-hand	Yes	100% is assumed for both exposure scenarios

Table 2-10. PBPK Model Input Parameters for Repackaging

Scenario	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Central Tendency	0.760	0.5	445 (f) 535 (m)	10	1	74 (f) 88 (m)
High-end	5.85	2.06	890 (f) 1,070 (m)	10	1	74 (f) 88 (m)

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed to liquid NMP of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Scenario	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Full-Shift NMP Air Concentration (mg/m^3, 8-hr TWA) [a]	Skin Surface Area Exposed (cm^2) [b]	Gloves Protection Factor	NMP Weight Fraction
Central Tendency	0.76	0.5	0.0475	445 (f) 535 (m)	10	1
High-end	5.85	2.06	1.51	890 (f) 1,070 (m)	10	1

[a] Calculated based on the duration-based air concentration and exposure duration, 8-hour TWA = (Duration-based air concentration) x (Exposure duration)/8 hours.
[b] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

Summary

In summary, dermal and inhalation exposures are expected for this use. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

EPA assessed dermal exposure to liquids using the most recent CDR data for concentration provided by industry submitters. Modeling, in the middle of the approach hierarchy, was used to estimate occupational inhalation exposure concentrations for both the unloading of NMP from bulk containers and from drums. For modeling of these air concentrations, EPA attempted to address variability in input parameters by estimating both central tendency and high-end parameter values. Additionally, for modeling of air concentrations during the loading of drums, EPA used Monte Carlo simulation to capture variability in input parameters. EPA expects the duration of inhalation and dermal exposure to be realistic, as the durations are based on the length of time to load NMP into specific container sizes (i.e., tank trucks, rail cars, and drums).

Primary Limitations

The representativeness of the estimates of duration of inhalation and dermal exposure for the unloading activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. NMP concentration is reported to CDR as a range and EPA assessed only the upper end of the range since a central value cannot be ascertained for this scenario. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage is likely based on professional judgment. The assumed glove protection factor values are uncertain. EPA is uncertain of the accuracy of the emission factors used to estimate fugitive NMP emissions and thereby to model NMP air concentrations. The representativeness of the modeling results toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium.

2.4.1.2.3 Chemical Processing, Excluding Formulation

This scenario includes the use of NMP for processing activities other than formulation (i.e., non-incorporative processing). Specifically, this may include the use of NMP as an intermediate, as a media for synthesis, extractions, and purifications, or as some other type of processing aid. EPA identified the following industries that use NMP in this manner (RIVM, 2013); (U.S. EPA, 2017c):

- Agricultural chemical manufacturing
- Petrochemical manufacturing
- Pharmaceutical manufacturing
- Polymer product manufacturing

For this industrial exposure scenario, EPA assessed inhalation, vapor-through-skin, and dermal exposures from the unloading of various containers (i.e., drums, tank trucks, rail cars) with pure NMP. While EPA does expect that workers may perform additional activities during this scenario, such as sampling or maintenance work, EPA expects that unloading activities present the largest range of potential exposures.

Inhalation and Vapor-through-Skin

EPA found limited monitoring data for the use of NMP in non-incorporative processing activities (e.g., use of NMP as an intermediate, as a media for synthesis, extractions, and purifications, or as some other type of processing aid), and the monitoring data found lacks data on worker activities, the function of NMP within the industry of use, and the sampling duration. Due to limited relevance and quality of monitoring data and modeling estimates for chemical processing with NMP found in the published literature, EPA used modeling estimates with the highest data quality for this use. The *Drum Loading and Unloading Release and Inhalation Exposure Model* involves probabilistic modeling.

The inhalation exposure concentrations modeled by EPA for loading of NMP are summarized into the input parameters used for the PBPK modeling in Table 2-11. The modeled exposure concentrations are the same as those for Manufacturing and Repackaging; however, the exposure durations are different because they are based on the NMP volume unloaded for the exposure scenario. Note that the exposure duration for the central tendency and high-end exposure scenarios are the same because the unloading

rate does not vary in this model. The supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r) provides additional details.

Table 2-11. Summary of Parameters for PBPK Modeling of Worker Inhalation Exposure During Chemical Processing

Work Activity	Parameter Characterization	Full-Shift NMP Air Concentration (mg/m^3, 8-hr TWA)	Duration-Based NMP Air Concentration (mg/m^3)	Source	Data Quality Rating
Unloading liquid NMP from drums	Central tendency (50th percentile)	0.075	1.65 (duration = 0.36 hr)	*Drum Loading and Unloading Release and Inhalation Exposure Model* (U.S. EPA, 2013a)	Not applicable[a]
	High-end (95th percentile)	0.265	5.85 (duration = 0.36 hr)		

a - EPA models are standard sources used by EPA for occupational exposure assessments. EPA did not systematically review models that were developed by EPA.

Dermal

Table 2-12 summarizes the parameters used to assess dermal exposure during NMP use in non-incorporative processing activities. EPA assessed dermal exposures during the unloading of pure NMP from drums. Most of these parameters were determined based on assumptions described in Section 2.4.1.1. EPA used data from 2016 CDR, public comments, and the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017) to determine the NMP weight fraction. The underlying data rated by EPA have data quality ratings of high. Because this scenario has only industrial sites, EPA assumes that workers are likely to wear protective gloves and have basic training on the proper usage of these gloves for both central and high-end exposures, corresponding to a protection factor of 10.

Table 2-12. Summary of Parameters for Worker Dermal Exposure to Liquids During Chemical Processing, Excluding Formulation

Work Activity	Parameter Characterization	Glove Protection Factor(s)	NMP Weight Fraction	Skin Surface Area Exposed [a]	Exposure Duration	Body Weight [a]
			Unitless	cm^2	hr/day	kg
Unloading liquid NMP from drums	Central Tendency	10	1	445 (f) 535 (m)	0.36	74 (f) 88 (m)
	High-End	10	1	890 (f) 1,070 (m)	0.36	

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

PBPK Inputs

EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-13.

The numeric parameters corresponding to the characterizations presented in Table 2-13 are summarized in Table 2-14. These are the inputs used in the PBPK model.

Table 2-13. Characterization of PBPK Model Input Parameters for Chemical Processing, Excluding Formulation

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	Unloading drums	Central tendency (50th percentile)	Duration calculated by model	1-hand	Yes	N/A - 100% is assumed for both exposure scenarios
High-end	Unloading drums	High-end (95th percentile)	Duration calculated by model	2-hand	Yes	N/A - 100% is assumed for both exposure scenarios

Table 2-14. PBPK Model Input Parameters for Chemical Processing, Excluding Formulation

Scenario	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Central Tendency	1.65	0.36	445 (f) 535 (m)	10	1	74 (f) 88 (m)
High-end	5.85	0.36	890 (f) 1,070 (m)	10	1	74 (f) 88 (m)

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed to liquid NMP of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Summary

In summary, dermal and inhalation exposures are expected for this use. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

EPA assessed dermal exposure to liquids using the most recent CDR data for concentration provided by industry submitters. Modeling, in the middle of the approach hierarchy, was used to estimate

occupational inhalation exposure concentrations for both the unloading of NMP from bulk containers and from drums. For modeling of these air concentrations, EPA attempted to address variability in input parameters by estimating both central tendency and high-end parameter values. Additionally, EPA used Monte Carlo simulation to capture variability in input parameters. EPA expects the duration of inhalation and dermal exposure to be realistic, as the duration is based on the length of time to load NMP into drums.

Primary Limitations

The representativeness of the estimates of duration of inhalation and dermal exposure for the unloading activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. NMP concentration is reported to CDR as a range and EPA assessed only the upper end of the range since a central value cannot be ascertained for this scenario. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage is likely based on professional judgment. The assumed glove protection factor values are uncertain. EPA is uncertain of the accuracy of the emission factors used to estimate fugitive NMP emissions and thereby to model NMP air concentrations. The representativeness of the modeling results toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium.

2.4.1.2.4 Incorporation into Formulation, Mixture, or Reaction Product

This scenario includes the use of NMP for incorporation into a formulation, mixture or reaction product, which refers to the process of mixing or blending of several raw materials to obtain a single product or preparation. The uses of NMP that may require incorporation into a formulation include adhesives, sealants, paints, coatings, inks, metal finishing chemicals, cleaning and degreasing products, agricultural products, and petrochemical products including lube oils.

For this industrial exposure scenario, EPA assessed inhalation, vapor-through-skin, and dermal exposures from the unloading of various containers (i.e., drums, tank trucks, rail cars) with pure NMP and from maintenance, bottling, shipping, and loading of NMP in formulations.

Inhalation and Vapor-through-Skin

EPA compiled inhalation monitoring data and modeled exposure concentration data for the incorporation of NMP into a formulation, mixture or reaction product. Because EPA favors the use of monitoring data over modeled data, monitoring data with the highest data quality was used to assess exposure for this use. EPA used the monitoring data for the central tendency and high-end full-shift worker exposure concentrations presented in Table 2-15.

In addition to this monitoring data, EPA also modeled short-term worker inhalation exposure from unloading NMP. The *Drum Loading and Unloading Release and Inhalation Exposure Model* involves probabilistic modeling. The concentrations obtained from modeling are summarized into the input parameters used for the PBPK modeling in Table 2-17 and Table 2-18. In addition to the formulation of liquid products, EPA identified formulation activities that may result in potential worker exposures to

solids containing NMP. EPA estimated inhalation exposure concentration of NMP in particulates; however, EPA does not use these exposure concentrations as input to the PBPK model because the PBPK model does not account for solids, and the range of input parameters for the other exposure scenarios capture these concentrations. The supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r) provides additional details.

Table 2-15. Summary of Parameters for PBPK Modeling of Worker Inhalation Exposure During Incorporation into Formulation, Mixture or Reaction Product

Work Activity	Parameter Characterization	Full-Shift NMP Air Concentration (mg/m^3, 8-hr TWA)	Duration-Based NMP Air Concentration (mg/m^3)	Source	Data Quality Rating
Unloading liquid NMP from drums	Central Tendency (50th percentile)	0.075	1.65 (duration = 0.36 hr)	*Drum Loading and Unloading Release and Inhalation Exposure Model* (U.S. EPA, 2013a)	Not applicable[a]
Maintenance, bottling, shipping, loading	High-end (95th percentile)	12.8	No data	(Bader et al., 2006)	High
Loading solids into drums	Central Tendency (50th percentile)	0.75	No data	EPA's OSHA PNOR PEL model (U.S. EPA, 2013a) and NMP concentration data	Not applicable
	High-end (95th percentile)	0.96	No data		

a - EPA models are standard sources used by EPA for occupational exposure assessments. EPA did not systematically review models that were developed by EPA.

Dermal

Table 2-16 summarizes the parameters used to assess dermal exposure during the incorporation of NMP into formulations, mixtures, and reaction products. For this life cycle stage, EPA assessed dermal exposures during the unloading of pure NMP from drums. As indicated above, the PBPK model does not account for solids so EPA did not include loading of solids in the dermal parameter summary. Most of these parameters were determined based on assumptions described in Section 2.4.1.1. EPA used data from 2016 CDR, public comments, literature, and the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017) to determine the NMP weight fraction. The underlying data rated by EPA have data quality ratings ranging from medium to high. Because this scenario has only industrial sites, EPA assumes that

workers are likely to wear protective gloves and have basic training on the proper usage of these gloves for both central and high-end exposures, corresponding to a protection factor of 10.

Table 2-16. Summary of Parameters for Worker Dermal Exposure to Liquids During Incorporation into Formulation, Mixture, or Reaction Product

Work Activity	Parameter Characterization	Glove Protection Factor(s)	NMP Weight Fraction	Skin Surface Area Exposed [a]	Exposure Duration	Body Weight [a]
			Unitless	cm^2	hr/day	kg
Unloading liquid NMP from drums	Central Tendency	10	1	445 (f) 535 (m)	0.36	74 (f) 88 (m)
Maintenance, bottling, shipping, loading	High-End	10	1	890 (f) 1,070 (m)	8	74 (f) 88 (m)

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

PBPK Inputs

EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-17. EPA only presents these scenarios for handling of liquid NMP, to present conservative assessments of potential exposures.

The numeric parameters corresponding to the characterizations presented in Table 2-17 are summarized in Table 2-18. These are the inputs used in the PBPK model.

Table 2-17. Characterization of PBPK Model Input Parameters for Incorporation into Formulation, Mixture or Reaction Product

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	Unloading drums	Central tendency (50^{th} percentile)	Duration calculated by model	1-hand	Yes	N/A - 100% is assumed for both exposure scenarios
High-end	Maintenance, bottling, shipping, loading	High-end (95^{th} percentile)	Duration calculated by model	2-hand	Yes	N/A - 100% is assumed for both exposure scenarios

Table 2-18. PBPK Model Input Parameters for Incorporation into Formulation, Mixture or Reaction Product

Scenario	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Hand Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Central Tendency	1.65	0.36	445 (f) 535 (m)	10	1	74 (f) 88 (m)
High-end	12.8	8	890 (f) 1,070 (m)	10	1	74 (f) 88 (m)

[a] Calculated based on the duration-based air concentration and exposure duration, 8-hour TWA = (Duration-based air concentration) x (Exposure duration)/8 hours.[b] EPA assessed these exposure factors for both females and males. [a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed to liquid NMP of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Summary

In summary, dermal and inhalation exposures are expected for this use. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

EPA assessed dermal exposure to liquids using the most recent CDR data for concentration provided by industry submitters. Modeling, in the middle of the approach hierarchy, was used to estimate occupational inhalation exposure concentrations for the unloading of NMP from drums. For modeling of these air concentrations, EPA attempted to address variability in input parameters by estimating both central tendency and high-end parameter values. Additionally, EPA used Monte Carlo simulation to capture variability in input parameters. EPA expects the duration of inhalation and dermal exposure to be realistic, as the duration is based on the length of time to load NMP into drums. EPA assessed worker inhalation exposure during maintenance, bottling, shipping, and loading of NMP using directly applicable monitoring data, which is the highest of the approach hierarchy, taken at an adhesive formulation facility. The data quality rating for the monitoring data used by EPA is high. EPA expects the duration of inhalation and dermal exposure to be realistic for the unloading of drums, as the duration is based on the length of time to load NMP into drums.

Primary Limitations

The representativeness of the estimates of duration of inhalation and dermal exposure for the assessed activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. NMP concentration is reported to CDR as a range and EPA assessed only the upper end of the range since a central value cannot be ascertained for this scenario (NMP concentration is lower in the formulated products). Skin surface areas for actual dermal contact are uncertain. EPA did

not find data on the use of gloves for this occupational exposure scenario and assumed glove usage is likely based on professional judgment. The assumed glove protection factor values are uncertain.

EPA estimated worker inhalation exposure concentration during the loading of NMP in solid formulations using EPA's OSHA PEL for PNOR model (U.S. EPA, 2013a), which is the lowest approach on the hierarchy. EPA did not use these inhalation exposure concentrations for the PBPK modeling because the PBPK model does not account for solids and because both the inhalation and dermal exposure potential are captured within other occupational exposure scenarios. EPA is uncertain of the accuracy of the emission factors used to estimate fugitive NMP emissions and thereby to model NMP air concentrations. For the maintenance, bottling, shipping, and loading of liquid NMP, the monitoring data consists of only 7 data points from 1 source. The representativeness of the modeling and the monitoring data toward the true distribution of inhalation concentrations for these occupational exposure scenarios is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium.

2.4.1.2.5 Metal Finishing

This scenario includes the use of metal finishing products containing NMP. For this industrial and commercial exposure scenario, EPA assessed inhalation, vapor-through-skin, and dermal exposures to metal finishing products containing NMP from the following application methods:

- Spray application;
- Dip application; and
- Brush application.

While EPA does expect that workers may perform additional activities during this scenario, such as unloading or sampling, EPA expects that application activities present the largest range of potential exposures.

Inhalation and Vapor-through-Skin

EPA compiled inhalation monitoring data for NMP-based metal finishing applications from published literature sources, including 8-hour TWA, short-term and partial shift sampling results. Where available, EPA used monitoring data for metal finishing or surrogate monitoring data (surrogate work activities using NMP) for the use of NMP during the Application of Paints, Coatings, Adhesives, and Sealants (Section 2.4.1.2.5) and Cleaning (Section 2.4.1.2.10) that had the highest quality rating to assess exposure. Where monitoring data were unavailable for an application type, EPA used modeling estimates with the highest data quality to assess exposure.

EPA found limited data on the application of metal finishing chemicals and thus assessed spray application using data from the Application of Paints, Coatings, Adhesives, and Sealants occupational exposure scenario (Section 2.4.1.2.5) as a surrogate for the worker activities in this occupational exposure scenario. EPA also used data for dip cleaning from the Cleaning occupational exposure scenario (Section 2.4.1.2.10) as a surrogate for the worker activities in this occupational exposure scenario. EPA used these data as surrogate because of the lack of more applicable data and due to the similarity in work activities (e.g., spray and dip activities are similar between these OESs) between the

occupational exposure scenarios. Finally, EPA used a modeled exposure estimate for the brush application of a substance containing NMP.

The monitoring data and the modeled exposure estimates for metal finishing are summarized according to the input parameters used for the PBPK modeling in Table 2-19. The supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r) provides additional details.

Table 2-19. Summary of Parameters for PBPK Modeling of Worker Inhalation Exposure During Metal Finishing

Work Activity	Parameter Characterization	Full-Shift NMP Air Concentration (mg/m^3, 8- hr TWA)	Duration-Based NMP Air Concentration (mg/m^3)	Source	Data Quality Rating
Spray Application	Low-end (of range)	0.04	0.04 (duration = 4 hr)	(NIOSH, 1998)	High
	Mean	0.53	0.53 (duration = 4 hr)		
	High-end (of range)	4.51	4.51 (duration = 4 hr)		
Dip Application	Central Tendency (50^{th} percentile)	0.99	No data	Surrogate data (surrogate work activities using NMP) from: (RIVM, 2013; Nishimura et al., 2009; Bader et al., 2006; Xiaofei et al., 2000) (IFA, 2010)	Medium to high
	High-end (95^{th} percentile)	2.75	No data		
Brush Application	Single estimate	4.13	No data	(RIVM, 2013)	High

Dermal

Table 2-20 summarizes the parameters used to assess dermal exposure during application of metal finishing formulations containing NMP. Most of these parameters were determined based on assumptions described in Section 2.4.1.1. EPA used data from the 2012 and 2016 CDR to determine the NMP weight fraction, which indicate that the weight concentration of NMP in formulation is greater than 60 percent but less than 90 percent. Due to lack of additional information, EPA assesses a low-end weight fraction of 0.6 and a high-end weight fraction of 0.9. The CDR data have a data quality rating of high. Because this scenario covers a variety of commercial and industrial sites, EPA assumes that either no gloves are used or, if gloves are used, that there is no permeation data to indicate the glove material is protective for NMP, corresponding to a protection factor of 1. EPA assesses a central tendency scenario

assuming the use of gloves with minimal to no employee training, corresponding to a protection factor of 5.

Table 2-20. Summary of Parameters for Worker Dermal Exposure to Liquids During Metal Finishing

Work Activity	Parameter Characterization	Glove Protection Factor(s)	NMP Weight Fraction	Skin Surface Area Exposed [a]	Exposure Duration	Body Weight [a]
			Unitless	cm^2	hr/day	kg
All forms of application listed above	Central Tendency	5	0.6	445 (f) 535 (m)	4	74 (f) 88 (m)
	High-end	1	0.9	890 (f) 1,070 (m)	8	

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

PBPK Inputs

EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-21.

The numeric parameters corresponding to the characterizations presented in Table 2-21 are summarized in Table 2-22. These are the inputs used in the PBPK model.

Table 2-21. Characterization of PBPK Model Input Parameters for Metal Finishing

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	Spray application	Mean	Assumed 4 hours	1-hand	Yes	Central Tendency
High-end	Spray application	High-end (of range)	Assumed 8 hours	2-hand	No	High-end
Central Tendency	Dip application	Central Tendency (50th percentile)	Assumed 4 hours	1-hand	Yes	Central Tendency
High-end	Dip application	High-end (95th percentile)	Assumed 8 hours	2-hand	No	High-end
Central Tendency	Brush application	Single estimate	Assumed 4 hours	1-hand	Yes	Central Tendency
High-end	Brush application	Single estimate	Assumed 8 hours	2-hand	No	High-end

Table 2-22. PBPK Model Input Parameters for Metal Finishing

Scenario	Work Activity	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Central Tendency	Spray application	0.530	4	445 (f) 535 (m)	5	0.6	74 (f) 88 (m)
High-end	Spray application	4.51	8	890 (f) 1,070 (m)	1	0.9	74 (f) 88 (m)
Central Tendency	Dip application	1.98	4	445 (f) 535 (m)	5	0.6	74 (f) 88 (m)
High-end	Dip application	2.75	8	890 (f) 1,070 (m)	1	0.9	74 (f) 88 (m)
Central Tendency	Brush application	8.26	4	445 (f) 535 (m)	5	0.6	74 (f) 88 (m)
High-end	Brush application	4.13	8	890 (f) 1,070 (m)	1	0.9	74 (f) 88 (m)

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed to liquid NMP of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Summary

In summary, dermal and inhalation exposures are expected for this use. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

EPA assessed dermal exposure to liquids using the most recent CDR data for concentration provided by industry submitters. To estimate inhalation exposure during spray application, EPA used surrogate monitoring data (surrogate work activities using NMP), which is in the middle of the approach hierarchy, including 26 data points. These data have a data quality rating of high. To estimate inhalation exposure during dip application, EPA used surrogate monitoring data for the use of NMP design dip cleaning, which is in the middle of the approach hierarchy, including data from 5 sources. These data have data quality ratings of medium to high. To estimate inhalation exposure during brush application, EPA used modeled data from the RIVM report (RIVM, 2013), which has a data quality rating of high. The use of modeling is in the middle of the approach hierarchy. EPA used durations associated with inhalation monitoring data to estimate duration of inhalation and dermal exposure during spray application.

Primary Limitations

EPA did not find exposure data for this occupational exposure scenario and used surrogate or modeled data to assess occupational inhalation exposures. For occupational exposure scenarios other than spray application, EPA did not find exposure duration data and assumed a high-end of 8 hours because the surrogate data or modeled values are 8-hour TWA values. EPA assumed a mid-range of 4 hours for central tendency exposure duration. The representativeness of the assumed estimates of duration of inhalation and dermal exposure for the assessed activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. Due to lack of data, EPA could not calculate central tendency and high-end NMP concentration in metal finishing products and used the low-end and high-end of the NMP concentration range reported in 2016 CDR. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with minimal to no employee training or no glove usage due to the potential wide-spread use of metal finishing products. The assumed glove protection factor values are uncertain. The available monitoring data for spray application is from 1996. The extent to which these data are representative of current worker inhalation exposure potential is uncertain. The worker activities associated with the surrogate data used to assess worker inhalation exposure during dip application are not detailed for all sample points. The modeled inhalation exposure concentration during roller/brush application was obtained from RIVM (2013) and not generated by EPA. For all occupational exposure scenarios, representativeness of the monitoring data, surrogate monitoring data, or modeled data toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium.

2.4.1.2.6 Removal of Paints, Coatings, Adhesives and Sealants

This scenario includes the use of paint, coating, adhesive, and sealant removal products containing NMP. For this industrial and commercial exposure scenario, EPA assessed inhalation, vapor-through-skin, and dermal exposures to paint, coating, adhesive, and sealant removal products containing NMP from the following activities:

- Miscellaneous paint and coating removal; and
- Graffiti removal.

While EPA does expect that workers may perform additional activities during this scenario, such as unloading or sampling, EPA expects that removal activities present the largest range of potential exposures.

Worker activities for the removal of paints, coatings, adhesives, and sealants involve the application of products containing high concentrations of NMP onto open surfaces from which evaporation will occur. This results in higher NMP air concentrations and potential worker exposures relative to other occupational exposure scenarios in this risk evaluation.

Inhalation and Vapor-through-Skin

EPA compiled inhalation monitoring data for NMP-based paint, coating, adhesive, and sealant removal from published literature sources, including 8-hour TWA, short-term, and partial shift sampling results. This data is summarized into low-end (lowest concentration), high-end (highest concentration), and mean or mid-range values in Table 2-23. EPA used the available monitoring data with the highest data quality to assess exposure for this use. The data presented in Table 2-23 are the input parameters used for the PBPK modeling for workers. The supplemental document Risk Evaluation *for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r) provides additional details.

Table 2-23. Summary of Parameters for PBPK Modeling of Worker Inhalation Exposure During Removal of Paints, Coatings, Adhesives and Sealants

Work Activity	Parameter Characterization	Full-Shift NMP Air Concentration (mg/m^3, 8-hr TWA)	Duration-Based NMP Air Concentration (mg/m^3)	Source	Data Quality Rating
Miscellaneous paint, coating, adhesive, and sealant removal	Low end (of range)	1.0	6.1 (duration = 1 hr)	(U.S. EPA, 2015)	High
	Mid-range	32.5	13.2 (duration = 1 hr)		
	High end (of range)	64	280 (duration = 1 hr)		
Graffiti removal	Low end (of range)	0.03	No data	(U.S. EPA, 2015)	High
	Mean	1.01	No data		
	High end (of range)	4.52	No data		

Dermal

Table 2-24 summarizes the parameters used to assess dermal exposure during paint, coating, adhesive, and sealant removal. Most of these parameters were determined based on assumptions described in Section 2.4.1.1. EPA used data from public comments, literature sources, and the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017) to determine the NMP weight fraction. The underlying data have data quality ratings ranging from medium to high. One anecdotal survey of glove usage among workers performing graffiti removal indicates that most workers wear gloves, although the glove materials varied and were sometimes not protective (U.S. EPA, 2015). Because this scenario covers a variety of commercial and industrial sites, EPA assumes that either no gloves are used or, if gloves are used, there is no permeation data to indicate the glove material is protective for NMP, corresponding to a protection factor of 1. EPA assesses a central tendency scenario assuming the use of gloves with minimal to no employee training, corresponding to a protection factor of 5.

Table 2-24. Summary of Parameters for PBPK Modeling of Worker Dermal Exposure to Liquids During Removal of Paints, Coatings, Adhesives and Sealants

Work Activity	Parameter Characterization	Glove Protection Factor(s)	NMP Weight Fraction	Skin Surface Area Exposed [a]	Exposure Duration	Body Weight [a]
			Unitless	cm^2	hr/day	kg
Miscellaneous paint, coating, adhesive, and sealant removal	Central Tendency	5	0.305	445 (f) 535 (m)	1	74 (f) 88 (m)
	High-End	1	0.695	890 (f) 1,070 (m)	8	
Graffiti removal	Central Tendency	5	0.5	445 (f) 535 (m)	4	74 (f) 88 (m)
	High-End	1	0.6125	890 (f) 1,070 (m)	8	

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

PBPK Inputs

EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-25.

The numeric parameters corresponding to the characterizations presented in Table 2-25 are summarized in Table 2-26. These are the inputs used in the PBPK model.

Table 2-25. Characterization of PBPK Model Input Parameters for Removal of Paints, Coatings, Adhesives and Sealants

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	Miscellaneous paint, coating, adhesive, and sealant removal	Mid-range	Based on 1-hr TWA data	1-hand	Yes	Central Tendency
High-end	Miscellaneous paint, coating, adhesive, and sealant removal	High-end (of range)	Assumed 8 hours	2-hand	No	High-end
Central Tendency	Graffiti removal	Mean	Assumed 4 hours	1-hand	Yes	Central Tendency
High-end	Graffiti removal	High-end (of range)	Assumed 8 hours	2-hand	No	High-end

Table 2-26. PBPK Model Input Parameters for Removal of Paints, Coatings, Adhesives and Sealants

Scenario	Work Activity	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Central Tendency	Miscellaneous paint, coating, adhesive, and sealant removal	13.2	1	445 (f) 535 (m)	5	0.305	74 (f) 88 (m)
High-end	Miscellaneous paint, coating, adhesive, and sealant removal	64	8	890 (f) 1,070 (m)	1	0.695	74 (f) 88 (m)
Central Tendency	Graffiti removal	2.02	4	445 (f) 535 (m)	5	0.5	74 (f) 88 (m)
High-end	Graffiti removal	4.52	8	890 (f) 1,070 (m)	1	0.613	74 (f) 88 (m)

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed to liquid NMP of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Summary

In summary, dermal and inhalation exposures are expected for this use. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

EPA assessed dermal exposure to central tendency and high-end NMP weight fractions, calculated as the 50th and 95th percentiles, respectively, from a variety of data sources with data quality ratings ranging from medium to high. To estimate inhalation exposure during miscellaneous paint and coating removal, EPA used directly applicable personal monitoring data, the highest of the approach hierarchy, including data from three studies. These data have a data quality rating of high. To estimate inhalation exposure during graffiti removal, EPA used directly applicable personal monitoring data, the highest of the approach hierarchy, including 25 data points. These data have a data quality rating of high. EPA used durations associated with inhalation monitoring data to estimate duration of inhalation and dermal exposure during miscellaneous paint, coating, adhesive, and sealant removal.

Primary Limitations

For graffiti removal, EPA did not find data other than 8-hour TWA values. EPA assumed a high-end exposure duration equal to 8 hours and a central tendency exposure duration of 4 hours, which is the mid-range of a full shift. The representativeness of the assumed estimates of duration of inhalation and dermal exposure for the assessed activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with minimal to no employee training or no glove usage due to the wide-spread use of removal products. The assumed glove protection factor values are uncertain.

The short-term inhalation exposure concentrations for miscellaneous removal are based on data from 1993 and the extent to which these data are representative of current worker inhalation exposure potential is uncertain. For graffiti removal, EPA used the minimum, mean, and maximum air concentrations reported by one literature source for 25 datapoints. EPA did not have these 25 data points with which to calculate 50th and 95th percentile values. The representativeness of the monitoring data toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium.

2.4.1.2.7 Application of Paints, Coatings, Adhesives and Sealants

This scenario includes the application of paints, coatings, adhesives, and sealants containing NMP. For this industrial and commercial exposure scenario, EPA assessed inhalation, vapor-through-skin, and dermal exposures to paints, coatings, adhesives, and sealants containing NMP from the following application methods:

- Spray application;
- Roll / curtain application;
- Dip application; and
- Roller / brush and syringe / bead application.

While EPA does expect that workers may perform additional activities during this scenario, such as unloading or sampling, EPA expects that application activities present the largest range of potential exposures.

Inhalation and Vapor-through-Skin

EPA compiled inhalation monitoring data and modeled exposure data for NMP-based paint, coating, adhesive, and sealant application from published literature sources, including 8-hour TWA, short-term, and partial shift sampling results. Where available, EPA compiled surrogate monitoring data (surrogate work activities using NMP) for the use of NMP during cleaning, which is described in Section 2.4.1.2.10. Where monitoring data were unavailable for an application type, EPA used surrogate monitoring data (surrogate work activities using NMP) or modeling estimates with the highest data quality to assess exposure, as further described below.

EPA found limited to no inhalation monitoring data on roll / curtain application, dip application, or roller /brush and syringe / bead application with NMP-containing formulations, so either surrogate data for the use of NMP during the Cleaning occupational exposure scenario or modeling data were used to determine the modeling parameters for these application methods. The *EPA/OPPT UV Roll Coating Model* was used for roll / curtain coating application and involved deterministic modeling.

The monitoring data and the modeled exposures for this life cycle stage are summarized in Table 2-27. The supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r) provides additional details.

Table 2-27. Summary of Parameters for PBPK Modeling of Worker Inhalation Exposure During Application

Work Activity	Parameter Characterization	Full-Shift NMP Air Concentration (mg/m^3, 8-hr TWA)	Duration-Based NMP Air Concentration (mg/m^3)	Source	Data Quality Rating
Spray Application	Low-end (of range)	0.04	0.04 (duration = 4 hr)	(NIOSH, 1998)	High
	Mean	0.53	0.53 (duration = 4 hr)		
	High-end (of range)	4.51	4.51 (duration = 4 hr)		
	Central Tendency (50^{th} percentile)	0.03	No data	*EPA/OPPT UV Roll Coating*	Not applicable[a]

Work Activity	Parameter Characterization	Full-Shift NMP Air Concentration (mg/m^3, 8-hr TWA)	Duration-Based NMP Air Concentration (mg/m^3)	Source	Data Quality Rating
Roll / Curtain Application	High-end (95th percentile)	0.19	No data	*Model (*U.S. EPA, 2013a*)*	
Dip Application	Central Tendency (50th percentile)	0.99	No data	Surrogate data (surrogate work activities using NMP) from: (RIVM, 2013; IFA, 2010; Nishimura et al., 2009; Bader et al., 2006; Xiaofei et al., 2000)	Medium to high
	High-end (95th percentile)	2.75	No data		
Roller / Brush and Syringe / Bead Application	Single estimate	4.13	No data	(RIVM, 2013)	High

a - EPA models are standard sources used by EPA for occupational exposure assessments. EPA did not systematically review models that were developed by EPA.

Dermal

Table 2-28 summarizes the parameters used to assess dermal exposure during application of paints, coatings, adhesives, and sealants containing NMP. Most of these parameters were determined based on assumptions described in Section 2.4.1.1. EPA used data from public comments, literature, and the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017) to determine the NMP weight fraction. The underlying data rated by EPA have data quality ratings ranging from medium to high. Because this scenario covers a variety of commercial and industrial sites, EPA assumes that either no gloves are used or, if gloves are used, there is no permeation data to indicate the glove material is protective for NMP, corresponding to a protection factor of 1. EPA assesses a central tendency scenario assuming the use of gloves with minimal to no employee training, corresponding to a protection factor of 5.

Table 2-28. Summary of Parameters for Worker Dermal Exposure to Liquids During Application of Paints, Coatings, Adhesives and Sealants

Work Activity	Parameter Characterization	Glove Protection Factor(s)	NMP Weight Fraction	Skin Surface Area Exposed [a]	Exposure Duration	Body Weight [a]
			Unitless	cm^2	hr/day	kg
All forms of application listed above	Central Tendency	5	0.02	445 (f) 535 (m)	4	74 (f) 88 (m)
	High-End	1	0.534	890 (f) 1,070 (m)	8	

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

PBPK Inputs

EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-29.

The numeric parameters corresponding to the characterizations presented in Table 2-29 are summarized in
Table 2-30. These are the inputs used in the PBPK model.

Table 2-29. Characterization of PBPK Model Input Parameters for Application of Paints, Coatings, Adhesives, and Sealants

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	Spray application	Mean	Based on 4-hr TWA data	1-hand	Yes	Central Tendency
High-end	Spray application	High-end (of range)	Based on 8-hr TWA data	2-hand	No	High-end
Central Tendency	Roll / curtain application	Central tendency (50^{th} percentile)	Assumed 4 hours	1-hand	Yes	Central Tendency
High-end	Roll / curtain application	High-end (95^{th} percentile)	Based on 8-hr TWA data	2-hand	No	High-end
Central Tendency	Dip application	Central tendency (50^{th} percentile)	Assumed 4 hours	1-hand	Yes	Central Tendency
High-end	Dip application	High-end (95^{th} percentile)	Based on 8-hr TWA data	2-hand	No	High-end

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	Brush application	Single estimate	Assumed 4 hours	1-hand	Yes	Central Tendency
High-end	Brush application	Single Estimate	Based on 8-hr TWA data	2-hand	No	High-end

Table 2-30. PBPK Model Input Parameters for Application of Paints, Coatings, Adhesives and Sealants

Scenario	Work Activity	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Glove Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Central Tendency	Spray application	0.530	4	445 (f) 535 (m)	5	0.02	74 (f) 88 (m)
High-end	Spray application	4.51	8	890 (f) 1,070 (m)	1	0.534	74 (f) 88 (m)
Central Tendency	Roll / curtain application	0.06	4	445 (f) 535 (m)	5	0.02	74 (f) 88 (m)
High-end	Roll / curtain application	0.19	8	890 (f) 1,070 (m)	1	0.534	74 (f) 88 (m)
Central Tendency	Dip application	1.98	4	445 (f) 535 (m)	5	0.02	74 (f) 88 (m)
High-end	Dip application	2.75	8	890 (f) 1,070 (m)	1	0.534	74 (f) 88 (m)
Central Tendency	Brush application	8.26	4	445 (f) 535 (m)	5	0.02	74 (f) 88 (m)
High-end	Brush application	4.13	8	890 (f) 1,070 (m)	1	0.534	74 (f) 88 (m)

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed to liquid NMP of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Summary

In summary, dermal and inhalation exposures are expected for this use. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

EPA assessed dermal exposure to central tendency and high-end NMP weight fractions, calculated as the 50th and 95th percentiles, respectively, from a variety of data sources with data quality ratings ranging from medium to high. To estimate inhalation exposure during spray application, EPA used directly applicable personal monitoring data, the highest of the approach hierarchy, including 26 data points. These data have a data quality rating of high. To estimate inhalation exposure during roll/curtain application, EPA used modeling, which is in the middle of the approach hierarchy. To estimate inhalation exposure during dip application, EPA used surrogate monitoring data for the use of NMP during dip cleaning, which is in the middle of the approach hierarchy, including data from 5 sources. These data have data quality ratings of medium to high. To estimate inhalation exposure during roller / brush and syringe/bead application, EPA used modeled data from the RIVM report (RIVM, 2013), which has a data quality rating of high. The use of modeling is in the middle of the approach hierarchy. EPA used durations associated with short-term inhalation monitoring data to estimate duration of inhalation and dermal exposure during spray application.

Primary Limitations

For occupational exposure scenarios other than spray application, EPA did not find exposure duration data and assumed a high-end of 8 hours because the surrogate data or modeled values are 8-hour TWA values. EPA assumed a mid-range of 4 hours for central tendency exposure duration. The representativeness of the assumed estimates of duration of inhalation and dermal exposure for the assessed activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with minimal to no employee training or no glove usage due to the wide-spread use of paint, coating, adhesive, and sealant products. The assumed glove protection factor values are uncertain.

The available monitoring data for spray application is from 1996 and the surrogate monitoring data used in the model for roll / curtain application is from 1994 or earlier. The extent to which these data are representative of current worker inhalation exposure potential is uncertain. The worker activities associated with the surrogate data (surrogate work activities using NMP) used to assess worker inhalation exposure during dip application are not detailed for all sample points. The modeled inhalation exposure concentration during roller / brush application was obtained from RIVM (2013) and not generated by EPA. For all occupational exposure scenarios, representativeness of the monitoring data, surrogate monitoring data, or modeled data toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium.

2.4.1.2.8 Electronic Parts Manufacturing

This scenario includes the use of NMP in the electronics industry. For this industrial exposure scenario, EPA assessed inhalation, vapor-through-skin, and dermal exposures to NMP from the following exposure scenarios during semiconductor manufacturing:

- Container handling (small containers);
- Container handling (drums);
- Workers in the fabrication shop;
- Maintenance activities;
- Virgin NMP truck unloading; and
- Waste NMP truck loading.

EPA expects that these activities present the largest range of potential exposures for use of NMP in the semiconductor manufacturing industry. While operations for the various types of electronics manufacturing that are included in this occupational exposure scenario may vary, EPA expects these activities in the semiconductor manufacturing industry are representative of the operating conditions expected at other electronic parts manufacturing facilities, due to the use of similarly controlled operations.

Inhalation and Vapor-through-Skin

Electronic parts manufacturing covers the use of NMP for lithium ion battery manufacturing, cleaning of electronic parts, coating of electronic parts, including magnet wire coatings, and photoresist and solder mask stripping. However, EPA only found inhalation monitoring data for the use of NMP in semiconductor manufacturing. Specifically, EPA uses data received from the Semiconductor Industry Association (SIA), which include full-shift personal breathing zone sampling results at semiconductor fabrication facilities during container handling of both small containers and drums, workers inside the fabrication rooms, maintenance workers, workers that unload trucks containing virgin NMP (100%), and workers that load trucks with liquid waste NMP (92%) (SIA, 2019).

The SIA monitoring data were summarized into the PBPK modeling full-shift input parameters in Table 2-31. The majority (96% of all samples) of samples in SIA (2019) were non-detect for NMP. Because the geometric standard deviation of the data set is greater than three, EPA used the limit of detection (LOD) divided by two to calculate central tendency and high-end values where samples were non-detect for NMP (U.S. EPA, 1994b). Due to the high amount of non-detect results, this method may result in bias. This is further described in the supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r). The SIA data included samples of both 8-hour TWA and 12-hour TWA values, with much of the data being 12-hour TWA. EPA used the 12-hour TWA values to assess occupational exposures in this occupational exposure scenario, as there is more data available for this exposure duration, indicating that typical shifts in this industry are 12 hours. Note, however, that the single data points available for the last two tasks in Table 2-31 are 8-hour TWA values.

Confidential data were submitted for an additional scenario for this industry and are not included in this evaluation.

Table 2-31. Summary of Parameters for PBPK Modeling of Worker Inhalation Exposure During Electronic Parts Manufacturing

Work Activity [a]	Parameter Characterization	Full-Shift NMP Air Concentration (mg/m^3, 12-hour TWA)	Duration-Based NMP Air Concentration (mg/m^3)	Source	Data Quality Rating
Container handling, small containers	Central tendency (50th percentile)	0.507	No data	(SIA, 2019)	High
	High-end (95th percentile)	0.608	No data		
Container handling, drums	Central tendency (50th percentile)	0.013	No data		
	High-end (95th percentile)	1.54	No data		
Fab worker	Central tendency (50th percentile)	0.138	No data		
	High-end (95th percentile)	0.405	No data		
Maintenance	Central tendency (50th percentile)	0.020	No data		
	High-end (95th percentile)	0.690	No data		
Virgin NMP truck unloading	Single value	4.78 [b]	No data		
Waste truck loading	Single value	0.709 [b]	No data		

[a] Electronic parts manufacturing includes the use of NMP for battery manufacturing, cleaning of electronic parts, coating of electronic parts, including magnet wire coatings, and photoresist and solder mask stripping.
[b] These are 8-hour TWA values.

Dermal

Table 2-32 summarizes the parameters used to assess dermal exposure during use of NMP in in the electronics industries. Most of these parameters were determined based on assumptions described in Section 2.4.1.1. EPA used data from SIA (2019), public comments, literature, and the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017) to determine the NMP weight fraction. The underlying data has a data quality rating of high. Because this scenario has only industrial sites, EPA assumes that workers are likely to wear protective gloves and have basic training on the proper usage of these gloves for both central and high-end exposures, corresponding to a protection factor of 10.

Table 2-32. Summary of Parameters for Worker Dermal Exposure During Electronic Parts Manufacturing

Work Activity [a]	Parameter Characterization	Glove Protection Factor(s)	NMP Weight Fraction	Skin Surface Area Exposed [b]	Exposure Duration	Body Weight [b]
			Unitless	cm^2	hr/day	kg
Container handling, small containers	Central Tendency	10	0.6	445 (f) 535 (m)	6	74 (f) 88 (m)
	High-End	10	0.75	890 (f) 1,070 (m)	12	
Container handling, drums	Central Tendency	10	0.5	445 (f) 535 (m)	6	74 (f) 88 (m)
	High-End	10	0.75	890 (f) 1,070 (m)	12	
Fab worker	Central Tendency	10	0.15	445 (f) 535 (m)	6	74 (f) 88 (m)
	High-End	10	0.999	890 (f) 1,070 (m)	12	
Maintenance	Central Tendency	10	0.55	445 (f) 535 (m)	6	74 (f) 88 (m)
	High-End	10	1	890 (f) 1,070 (m)	12	
Virgin NMP truck unloading	Central Tendency	10	1	445 (f) 535 (m)	4	74 (f) 88 (m)
	High-End	10	1	890 (f) 1,070 (m)	8	
Waste truck loading	Central Tendency	10	0.92	445 (f) 535 (m)	4	74 (f) 88 (m)
	High-End	10	0.92	890 (f) 1,070 (m)	8	

[a] Electronic parts manufacturing includes the use of NMP for battery manufacturing, cleaning of electronic parts, coating of electronic parts, including magnet wire coatings, and photoresist and solder mask stripping.
[b] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

PBPK Inputs

EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-33.

The numeric parameters corresponding to the characterizations presented in Table 2-33 are summarized in Table 2-34. These are the inputs used in the PBPK model.

Table 2-33. Characterization of PBPK Model Input Parameters for Electronic Parts Manufacturing

Scenario	Work Activity [a]	Air Concentration Data Characterization [b]	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	All activities	Central tendency (50th percentile)	Mid-point of shift duration	1-hand	Yes	Central tendency
High-end	All activities	High-end (95th percentile)	High-end of shift duration	2-hand	Yes	High-end

[a] Electronic parts manufacturing includes the use of NMP for battery manufacturing, cleaning of electronic parts, coating of electronic parts, including magnet wire coatings, and photoresist and solder mask stripping.
[b] Only a single estimate was available for virgin NMP truck unloading and waste truck loading. This single air concentration value was used with both central tendency and high-end duration and dermal parameters.

Table 2-34. PBPK Model Input Parameters for Electronic Parts Manufacturing

Work Activity	Scenario	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Container handling, small containers	Central Tendency	1.01	6	445 (f) 535 (m)	10	0.6	74 (f) 88 (m)
	High-end	0.608	12	890 (f) 1,070 (m)	10	0.75	74 (f) 88 (m)
Container handling, drums	Central Tendency	0.026	6	445 (f) 535 (m)	10	0.5	74 (f) 88 (m)
	High-end	1.54	12	890 (f) 1,070 (m)	10	0.75	74 (f) 88 (m)
Fab Worker	Central Tendency	0.276	6	445 (f) 535 (m)	10	0.15	74 (f) 88 (m)
	High-end	0.405	12	890 (f) 1,070 (m)	10	0.999	74 (f) 88 (m)
Maintenance	Central Tendency	0.040	6	445 (f) 535 (m)	10	0.55	74 (f) 88 (m)
	High-end	0.690	12	890 (f) 1,070 (m)	10	1	74 (f) 88 (m)
Virgin NMP truck unloading	Central tendency	9.56	4	445 (f) 535 (m)	10	1	74 (f) 88 (m)
	High-end	4.78	8	890 (f) 1,070 (m)	10	1	74 (f) 88 (m)
Waste truck loading	Central tendency	1.42	4	445 (f) 535 (m)	10	0.92	74 (f) 88 (m)
	High-end	0.709	8	890 (f) 1,070 (m)	10	0.92	74 (f) 88 (m)

Work Activity	Scenario	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed to liquid NMP of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Summary

In summary, dermal and inhalation exposures are expected for this use. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

EPA assessed dermal exposure to central tendency and high-end NMP weight fractions, calculated as the 50th and 95th percentiles, respectively, from the data provided by SIA (2019), which has a data quality rating of high. EPA used directly applicable inhalation monitoring data, which is the highest of the approach hierarchy, to estimate worker inhalation exposure during a variety of semiconductor manufacturing tasks. These data include over one hundred data points and have a data quality rating of high.

Primary Limitations

The SIA (2019) monitoring data were provided as 8-hour or 12-hour TWA values. EPA assumed 8 or 12 hours as the high-end exposure duration and mid-range of 4 or 6 hours as the central tendency exposure duration. The representativeness of the estimates of duration of inhalation and dermal exposure for the assessed activities toward the true distribution of duration for all worker activities in this occupational exposure scenario beyond semiconductor manufacturing is uncertain. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage is likely based on professional judgment, due to the highly controlled nature of electronics manufacturing. The assumed glove protection factor values are uncertain.

The majority of the data points in SIA (2019) were non-detect for NMP and, for these samples, EPA used the LOD/2 to calculate central tendency and high-end inhalation exposure concentration values. Due to the high amount of non-detect results, this method may result in bias. The representativeness of the monitoring data for semiconductor manufacturing toward the true distribution of inhalation concentrations for all worker activities in this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium.

2.4.1.2.9 Printing and Writing

This scenario includes printing and writing with inks containing NMP. For this industrial and commercial exposure scenario, EPA assessed inhalation, vapor-through-skin, and dermal exposures to inks containing NMP during printing activities. Additionally, EPA assessed dermal exposures to inks containing NMP during writing activities.

While EPA does expect that workers may perform additional activities during this scenario, such as unloading or maintenance activities, EPA expects that printing and writing activities present the largest range of potential exposures.

Inhalation and Vapor-through-Skin

EPA did not find inhalation monitoring data for the use of NMP-based printing inks. For printing activities, EPA used ink mist concentration data from a NIOSH Health Hazard Evaluation at a newspaper printing shop, with assumed NMP concentrations, to assess potential inhalation exposures in this occupational exposure scenario. Of the available data, this surrogate data has the highest quality; thus, EPA used this data to assess exposure for this use.

EPA did not find inhalation monitoring data for the use of writing utensils containing NMP. EPA did not assess potential inhalation exposures during the use of NMP-based writing inks based on information indicating these exposures may be negligible from a NICNAS assessment (NICNAS, 2016) and the likely outdoor use of the one writing product that was identified (weather-resistant marker).

The monitoring data presented in Table 2-35 represent input parameters used for the PBPK modeling. The supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r) provides additional details.

Table 2-35. Summary of Parameters for PBPK Modeling of Worker Inhalation Exposure During Printing and Writing

Work Activity	Parameter Characterization	Full-Shift NMP Air Concentration (mg/m^3, 8-hr TWA)	Duration-Based NMP Air Concentration (mg/m^3)	Source	Data Quality Rating
Printing	Central tendency (50th percentile)	0.018	0.016 (duration = 4 hr)	(Belanger and Coye, 1983)	Medium
	High-end (95th percentile)	0.172	0.042 (duration = 4 hr)		
Writing	Not assessed				

Dermal

Table 2-36 summarizes the parameters used to assess dermal exposure during printing and writing activities. Most of these parameters were determined based on assumptions described in Section 2.4.1.1. EPA used data from public comments and the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017) to determine the NMP weight fraction. The underlying data have a data quality rating of high. Because writing inks are contained within markers and pens, EPA expects the surface area of skin

potentially exposed to NMP to be smaller than the surface area of one or two hands. EPA used data from Australian Government Department of Health (2016), which has a data quality rating of medium, for the skin surface area exposed during writing. Because this scenario covers a variety of commercial and industrial sites, EPA assumes that either no gloves are used or, if gloves are used, there is no permeation data to indicate the glove material is protective for NMP, corresponding to a protection factor of 1. EPA assesses a central tendency scenario assuming the use of gloves with minimal to no employee training, corresponding to a protection factor of 5.

Table 2-36. Summary of Parameters for Worker Dermal Exposure to Liquids During Printing and Writing

Work Activity	Parameter Characterization	Glove Protection Factor(s)	NMP Weight Fraction	Skin Surface Area Exposed [a]	Exposure Duration	Body Weight [a]
			Unitless	cm^2	hr/day	kg
Printing	Central Tendency	5	0.05	445 (f) 535 (m)	4	74 (f) 88 (m)
	High-End	1	0.07	890 (f) 1,070 (m)	8	
Writing	Central Tendency	5	0.1	1 [b]	0.5	74 (f) 88 (m)
	High-End	1	0.2	1 [b]	0.5	

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] This surface area was assumed for both males and females based on (NICNAS, 2016).

PBPK Inputs

EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-37.

The numeric parameters corresponding to the characterizations presented in Table 2-37 are summarized in Table 2-38. These are the inputs used in the PBPK model.

Table 2-37. Characterization of PBPK Model Input Parameters for Printing and Writing

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed (cm^2)	Gloves	NMP Weight Fraction Characterization
Central Tendency	Printing	Central tendency (50^{th} percentile)	Based on 4-hr TWA data	1-hand	Yes	Central tendency
High-end	Printing	High-end (95^{th} percentile)	Based on 8-hr TWA data	2-hand	No	High-end

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed (cm^2)	Gloves	NMP Weight Fraction Characterization
Central Tendency	Writing	Inhalation exposure not assessed	Based on one contact event	1 cm^2	Yes	Central tendency
High-end	Writing	Inhalation exposure not assessed	Based on one contact event	1 cm^2	No	High-end

Table 2-38. PBPK Model Input Parameters for Printing and Writing

Scenario	Work Activity	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Central Tendency	Printing	0.016	4	445 (f) 535 (m)	5	0.05	74 (f) 88 (m)
High-end	Printing	0.172	8	890 (f) 1,070 (m)	1	0.07	74 (f) 88 (m)
Central Tendency	Writing	0	0.5	1	5	0.1	74 (f) 88 (m)
High-end	Writing	0	0.5	1	1	0.2	74 (f) 88 (m)

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed to liquid NMP of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Summary

In summary, dermal and inhalation exposures are expected for use of NMP in printing. Only dermal exposure is expected for use of NMP in writing activities. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

For printing activities, EPA assessed dermal exposure to central tendency and high-end NMP weight fractions, calculated as the 50th and 95th percentiles, respectively, from a variety of data sources with data quality ratings of high. For writing activities, EPA assessed dermal exposure to 10 to 20% NMP based on one writing product identified in the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017). For worker dermal exposure during writing, EPA determined the skin surface area dermally exposed to writing ink using a literature source with a data quality rating of high. To estimate worker

inhalation exposure during printing, EPA used surrogate monitoring data, which is in the middle of the approach hierarchy. These data include 48 samples and have a data quality rating of high. EPA used durations associated with inhalation monitoring data to estimate duration of inhalation and dermal exposure during printing activities.

Primary Limitations

For writing, EPA did not find exposure duration data and assumed a high-end of 8 hours based on the length of a full shift and a central tendency of 4 hours based on the mid-range of a shift. The representativeness of the assumed estimates of duration of inhalation and dermal exposure for the assessed printing and writing activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. For printing, skin surface areas for actual dermal contact are uncertain. EPA did not find data on glove usage. For printing activities, EPA assumed glove usage with minimal to no employee training or no glove usage due to the wide-spread use of ink products. The assumed glove protection factor values are uncertain. For writing activities, EPA assumed glove usage is unlikely for the use of markers based on professional judgment. The surrogate monitoring data used to estimate occupational inhalation exposure during printing is from 1983. The extent to which these data are representative of current worker inhalation exposure potential is uncertain. The representativeness of the surrogate monitoring data toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium.

2.4.1.2.10 Soldering

This scenario includes soldering with solder materials containing NMP. For this industrial and commercial exposure scenario, EPA assessed dermal exposures to NMP during soldering.

While EPA does expect that workers may perform additional activities during this scenario, such as equipment maintenance activities, EPA expects that soldering presents the largest range of potential exposures.

Inhalation and Vapor-through-Skin

Due to the low NMP content in the one identified soldering production containing NMP (1 to 2.5 weight percent NMP), the potential for worker inhalation exposures is likely small. In addition, some of the NMP may be destroyed in the soldering process, further mitigating the potential for inhalation exposures. EPA therefore did not assess inhalation and vapor-through-skin exposures for this occupational exposure scenario.

Dermal

Table 2-39 summarizes the parameters used to assess dermal exposure during the use of soldering products containing NMP. Most of these parameters were determined based on assumptions described in Section 2.4.1.1. EPA used data from the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017) to determine the NMP weight fraction. Because this scenario covers a variety of commercial and industrial sites, EPA assumes that either no gloves are used or, if gloves are used, there is no permeation data to indicate the glove material is protective for NMP, corresponding to a protection factor of 1. EPA

assesses a central tendency scenario assuming the use of gloves with minimal to no employee training, due to the widespread nature of this occupational exposure scenario, corresponding to a protection factor of 5.

Table 2-39. Summary of Parameters for Worker Dermal Exposure During Soldering

Work Activity	Parameter Characterization	Glove Protection Factor(s)	NMP Weight Fraction	Skin Surface Area Exposed [a]	Exposure Duration	Body Weight [a]
			Unitless	cm^2	hr/day	kg
Soldering	Central Tendency	5	0.01	445 (f) 535 (m)	4	74 (f) 88 (m)
	High-end	1	0.025	890 (f) 1,070 (m)	8	

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

PBPK Inputs

EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-40.

The numeric parameters corresponding to the characterizations presented in Table 2-40 are summarized in Table 2-41. These are the inputs used in the PBPK model.

Table 2-40. Characterization of PBPK Model Input Parameters for Soldering

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	Soldering	Inhalation Exposure Not Assessed	Assumed 4 hours	1-hand	Yes	Central Tendency
High-end	Soldering	Inhalation Exposure Not Assessed	Assumed 8 hours	2-hand	No	High-end

Table 2-41. PBPK Model Input Parameters for Soldering

Scenario	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Central Tendency	0	4	445 (f) 535 (m)	5	0.01	74 (f) 88 (m)
High-end	0	8	890 (f) 1,070 (m)	1	0.025	74 (f) 88 (m)

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed to liquid NMP of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Summary

In summary, only dermal exposure is expected for this use. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

EPA assessed worker dermal exposure to 1 – 2.5% NMP based on one soldering product identified in the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017). EPA did not assess occupational inhalation exposure because most NMP may be destroyed in the soldering process, mitigating the potential for significant inhalation exposures.

Primary Limitations

EPA did not find exposure duration data and assumed a high-end of 8 hours based on the length of a full shift and a central tendency of 4 hours based on the mid-range of a shift. The representativeness of the assumed estimates of duration of inhalation and dermal exposure toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with minimal to no employee training or no glove usage due to the commercial nature of this use. The assumed glove protection factor values are uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is low to medium.

2.4.1.2.11 Commercial Automotive Servicing

This scenario includes automotive servicing with products containing NMP. For this commercial exposure scenario, EPA assessed inhalation, vapor-through-skin, and dermal exposures to products containing NMP during aerosol degreasing of automotive brakes.

While EPA does expect that workers may perform additional activities during this scenario, such as unloading or sampling, EPA expects that aerosol degreasing activities present the largest range of potential exposures.

Inhalation and Vapor-through-Skin

EPA did not find monitoring data for the use of NMP products during automotive servicing. Because EPA did not find relevant monitoring data for this use in the published literature, modeling estimates were used to assess exposure for this use, as described below.

In lieu of monitoring data, EPA modeled potential occupational inhalation exposures for workers using EPA's model for Occupational Exposures during Aerosol Degreasing of Automotive Brakes. The *Occupational Exposures during Aerosol Degreasing of Automotive Brakes Model* involves probabilistic modeling. This model uses a near-field/far-field approach, where an aerosol application located inside the near-field generates a mist of droplets, and indoor air movements lead to the convection of the droplets between the near-field and far-field. Workers are assumed to be exposed to NMP droplet concentrations in the near-field, while ONUs are exposed at concentrations in the far-field. Consistent with the approach for other OESs, EPA uses the central tendency worker air concentration to evaluate ONU exposure and further refines this estimate using far-field modeling or applicable area monitoring data if the ONU MOE was below the benchmark MOE. Refinement was not necessary for this OES since the ONU MOE was above the benchmark MOE. The supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r) includes background information on this model, including model results and EPA's rationale for using it.

Table 2-42. Summary of Parameters for PBPK Modeling of Worker Inhalation Exposure During Commercial Automotive Servicing

Work Activity	Parameter Characterization	Full-Shift NMP Air Concentration (mg/m^3, 8-hr TWA)	Duration-Based NMP Air Concentration (mg/m^3)	Source	Data Quality Rating
Aerosol Degreasing	Central tendency (50th percentile)	6.39	19.96 (duration = 1 hr)	*Occupational Exposures during Aerosol Degreasing of Automotive Brakes Model*	Not applicable[a]
	High-end (95th percentile)	43.4	128.8 (duration = 1 hr)		

a - EPA models are standard sources used by EPA for occupational exposure assessments. EPA did not systematically review models that were developed by EPA.

Dermal

Table 2-43 summarizes the parameters used to assess dermal exposure during cleaning activities. Most of these parameters were determined based on assumptions described in Section 2.4.1.1. EPA used data from public comments and the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017) to determine the NMP weight fraction. The underlying data have a data quality rating of high. Because this scenario covers a variety of commercial and industrial sites, EPA assumes that either no gloves are used

or, if gloves are used, there is no permeation data to indicate the glove material is protective for NMP, corresponding to a protection factor of 1. EPA assesses a central tendency scenario assuming the use of gloves with minimal to no employee training, corresponding to a protection factor of 5.

Table 2-43. Summary of Parameters for Worker Dermal Exposure to Liquids During Commercial Automotive Servicing

Work Activity	Parameter Characterization	Glove Protection Factor(s)	NMP Weight Fraction	Skin Surface Area Exposed [a]	Exposure Duration	Body Weight [a]
			Unitless	cm^2	hr/day	kg
Commercial Automotive Servicing	Central Tendency	5	0.025	445 (f) 535 (m)	1	74 (f) 88 (m)
	High-end	1	0.33	890 (f) 1,070 (m)	8	

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

PBPK Inputs

EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-44.

The numeric parameters corresponding to the characterizations presented in Table 2-44 are summarized in Table 2-45. These are the inputs used in the PBPK model.

Table 2-44. Characterization of PBPK Model Input Parameters for Commercial Automotive Servicing

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	Aerosol degreasing	Central tendency (50^{th} percentile)	Based on time for one job	1-hand	Yes	Central Tendency
High-end	Aerosol degreasing	High-end (95^{th} percentile)	Assumed 8 hours	2-hand	No	High-end

Table 2-45. PBPK Model Input Parameters for Commercial Automotive Servicing

Scenario	Work Activity	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Central Tendency	Aerosol degreasing	19.96	1	445 (f) 535 (m)	5	0.025	74 (f) 88 (m)
High-end	Aerosol degreasing	43.4	8	890 (f) 1,070 (m)	1	0.33	74 (f) 88 (m)

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed to liquid NMP of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Summary

In summary, dermal and inhalation exposures are expected for this use. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

EPA assessed dermal exposure to central tendency and high-end NMP weight fractions, calculated as the 50th and 95th percentiles, respectively, from a variety of data sources with data quality ratings of high. Modeling, in the middle of the approach hierarchy, was used to estimate occupational inhalation exposure concentrations. For modeling of these air concentrations, EPA attempted to address variability in input parameters by estimating both central tendency and high-end parameter values. Additionally, EPA used Monte Carlo simulation to capture variability in input parameters. EPA expects the duration of inhalation and dermal exposure to be realistic, as the duration is based on the length of time to conduct aerosol degreasing of automotive brakes.

Primary Limitations

The representativeness of the estimates of duration of inhalation and dermal exposure for the aerosol brake degreasing activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with minimal to no employee training or no glove usage due to the wide-spread use of degreasing products. The assumed glove protection factor values are uncertain. For the modeling of NMP air concentrations, EPA used aerosol product use rate and application frequency from one literature source (CARB, 2000) on brake servicing. The extent to which this is representative of other aerosol degreasing applications involving NMP is uncertain. The representativeness of the modeling results toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence
Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium.

2.4.1.2.12 Laboratory Use

This scenario includes the use of NMP in a laboratory setting. For this industrial and commercial exposure scenario, EPA assessed inhalation, vapor-through-skin, and dermal exposures to 100% NMP during laboratory activities.

While EPA does expect that workers may perform additional activities during this scenario, such as unloading, EPA expects that laboratory use activities present the largest range of potential exposures.

Inhalation and Vapor-through-Skin
EPA only found one data source that had inhalation monitoring data, representing the preparation of NMP for use in samples, sample preparation involving the dissolving of solids in NMP, and sample analysis. These data were used as input into the PBPK model for 2-hour exposure duration. EPA did not find additional monitoring data, thus used a modeled exposure for the use of NMP in a laboratory setting for the full-shift concentrations. As the quality of both the monitoring and modeled data is acceptable, EPA used all available data to assess this occupational exposure scenario.

The monitoring data and modeled exposure summarized in Table 2-46 are the input parameters used for the PBPK modeling. The supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r) provides additional details.

Table 2-46. Summary of Parameters for PBPK Modeling of Worker Inhalation Exposure During Laboratory Use

Work Activity	Parameter Characterization	Full-Shift NMP Air Concentration (mg/m^3, 8-hr TWA)	Duration-Based NMP Air Concentration (mg/m^3)	Source	Data Quality Rating
Laboratory Use	Central tendency (unknown statistical characterization)	2.07	0.200 (duration = 2 hr)	(Solomon et al., 1996)	Medium
	High-end (unknown statistical characterization)	4.13	No data	(RIVM, 2013)	High

Dermal
Table 2-47 summarizes the parameters used to assess dermal exposure during use of NMP in laboratories. Most of these parameters were determined based on assumptions described in Section 2.4.1.1. Because NMP is used as a carrier chemical, EPA expects that NMP may be used in pure form (i.e., 100 percent NMP). Because laboratories have procedures and trainings to ensure accuracy and

quality of the performed analyses, EPA assumes that workers are likely to wear protective gloves and have basic training on the proper usage of these gloves, corresponding to a protection factor of 10.

Table 2-47. Summary of Parameters for Worker Dermal Exposure During Laboratory Use

Work Activity	Parameter Characterization	Glove Protection Factor(s)	NMP Weight Fraction	Skin Surface Area Exposed [a]	Exposure Duration	Body Weight [a]
			Unitless	cm^2	hr/day	kg
Laboratory Use	Central tendency	10	1	445 (f) 535 (m)	2	74 (f) 88 (m)
	High-end	10	1	890 (f) 1,070 (m)	8	

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

PBPK Inputs

EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-48.

The numeric parameters corresponding to the characterizations presented in Table 2-48 are summarized in Table 2-49. These are the inputs used in the PBPK model.

Table 2-48. Characterization of PBPK Model Input Parameters by Laboratory Use

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	Laboratory activities	Central tendency (unknown statistical characterization)	Based on 2-hr TWA data	1-hand	Yes	N/A - 100% is assumed for both exposure scenarios
High-end	Laboratory activities	High-end (unknown statistical characterization)	Assumed 8 hours	2-hand	Yes	N/A - 100% is assumed for both exposure scenarios

Table 2-49. PBPK Model Input Parameters for Laboratory Use

Scenario	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Central Tendency	0.200	2	445 (f) 535 (m)	20	1	74 (f) 88 (m)
High-end	4.13	8	890 (f) 1,070 (m)	20	1	74 (f) 88 (m)

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed to liquid NMP of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Summary

In summary, dermal and inhalation exposures are expected for this use. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

EPA assessed occupational inhalation exposure using directly applicable personal monitoring data, which is the highest of the approach hierarchy, from one source with a data quality rating of medium. EPA also used a modeled inhalation exposure concentration value, which is in the middle of the approach hierarchy, from RIVM (2013). This data has a data quality rating of high. EPA determined central tendency exposure duration from the inhalation monitoring data. EPA expects the central tendency duration of inhalation and dermal exposure to be realistic, as the duration is task-based.

Primary Limitations

EPA assumed a high-end exposure duration of 8 hours based on the length of a full shift. The representativeness of the assumed estimates of duration of inhalation and dermal exposure for the assessed activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. EPA did not find NMP concentration data and assumed workers may be exposed to up to 100% NMP since NMP is a carrier chemical, and carrier chemical concentrations may be very high. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage is likely based on professional judgment, due to safety and quality standards in laboratories. The assumed glove protection factor values are uncertain.

The monitoring data used for central tendency worker inhalation exposure is only one data point from a 1996 industrial hygiene report. The extent to which these data are representative of current worker inhalation exposure potential is uncertain. The modeled high-end inhalation exposure concentration was obtained from RIVM (2013) and not generated by EPA. The representativeness of the monitoring data

and modeled exposure toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium.

2.4.1.2.13 Cleaning

This scenario includes the use of cleaning products containing NMP. For this industrial and commercial exposure scenario, EPA assessed inhalation, vapor-through-skin, and dermal exposures to cleaning products containing NMP from the following activities:

- Dip cleaning / degreasing; and
- Spray / wipe cleaning.

While EPA does expect that workers may perform additional activities during this scenario, such as unloading or sampling, EPA expects that cleaning activities present the largest range of potential exposures.

Inhalation and Vapor-through-Skin

EPA compiled inhalation monitoring data and modeled exposure concentration data for NMP-based cleaning activities from published literature and used these data for the central tendency and high-end (for full-shift) worker exposure concentrations presented in Table 2-50. EPA used the available monitoring data for NMP use in cleaning that had the highest quality rating to assess exposure via this use. The supplemental document *Risk Evaluation for N-Methylpyrrolidone (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r) provides additional details.

Table 2-50. Summary of Parameters for PBPK Modeling of Worker Inhalation Exposure During Cleaning

Work Activity	Parameter Characterization	Full-Shift NMP Air Concentration (mg/m^3, 8-hr TWA)	Duration-Based NMP Air Concentration (mg/m^3)	Source	Data Quality Rating
Dip Cleaning / Degreasing	Central tendency (50th percentile)	0.99	No data	(RIVM, 2013; IFA, 2010; Nishimura et al., 2009; Bader et al., 2006; Xiaofei et al., 2000)	Medium to high
	High-end (95th percentile)	2.75	No data		
Spray / Wipe Cleaning	Central tendency (50th percentile)	1.01	No data	(RIVM, 2013; IFA, 2010; Nishimura et al., 2009; Bader et al., 2006)	Medium to high
	High-end (95th percentile)	3.38	No data		

Dermal

Table 2-51 summarizes the parameters used to assess dermal exposure during cleaning activities. Most of these parameters were determined based on assumptions described in Section 2.4.1.1. EPA used data from public comments, literature sources, and the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017) to determine the NMP weight fraction. The underlying data have data quality ratings ranging from medium to high. Because this scenario covers a variety of commercial and industrial sites, EPA assumes that either no gloves are used or, if gloves are used, there is no permeation data to indicate the glove material is protective for NMP, corresponding to a protection factor of 1. EPA assesses a central tendency scenario assuming the use of gloves with minimal to no employee training, corresponding to a protection factor of 5.

Table 2-51. Summary of Parameters for Worker Dermal Exposure to Liquids During Cleaning

Work Activity	Parameter Characterization	Glove Protection Factor(s)	NMP Weight Fraction	Skin Surface Area Exposed [a]	Exposure Duration	Body Weight [a]
			Unitless	cm^2	hr/day	kg
Dip Cleaning and Degreasing	Central Tendency	5	0.845	445 (f) 535 (m)	4	74 (f) 88 (m)
	High-End	1	0.999	890 (f) 1,070 (m)	8	
Spray/Wipe Cleaning	Central Tendency	5	0.313	445 (f) 535 (m)	4	74 (f) 88 (m)
	High-End	1	0.989	890 (f) 1,070 (m)	8	

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

PBPK Inputs

EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-52. The numeric parameters corresponding to the characterizations presented in Table 2-52 are summarized in Table 2-53. These are the inputs used in the PBPK model.

Table 2-52. Characterization of PBPK Model Input Parameters for Cleaning

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	Dip cleaning	Central tendency (50^{th} percentile)	Assumed 4 hours	1-hand	Yes	Central Tendency
High-end	Dip cleaning	High-end (95^{th} percentile)	Assumed 8 hours	2-hand	No	High-end
Central Tendency	Spray / wipe cleaning	Central tendency (50^{th} percentile)	Assumed 4 hours	1-hand	Yes	Central Tendency

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
High-end	Spray / wipe cleaning	High-end (95th percentile)	Assumed 8 hours	2-hand	No	High-end

Table 2-53. PBPK Model Input Parameters for Cleaning

Scenario	Work Activity	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Central Tendency	Dip cleaning	1.98	4	445 (f) 535 (m)	5	0.845	74 (f) 88 (m)
High-end	Dip cleaning	2.75	8	890 (f) 1,070 (m)	1	0.999	74 (f) 88 (m)
Central Tendency	Spray / wipe cleaning	2.02	4	445 (f) 535 (m)	5	0.313	74 (f) 88 (m)
High-end	Spray / wipe cleaning	3.38	8	890 (f) 1,070 (m)	1	0.989	74 (f) 88 (m)

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed to liquid NMP of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Summary

In summary, dermal and inhalation exposures are expected for this use. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

EPA assessed dermal exposure to central tendency and high-end NMP weight fractions, calculated as the 50th and 95th percentiles, respectively, from a variety of data sources with data quality ratings ranging from medium to high. To estimate inhalation exposure during dip cleaning, EPA used directly applicable monitoring data, which is in the highest of the approach hierarchy, including data from 5 sources. These data have data quality ratings ranging from medium to high. To estimate inhalation exposure during spray / wipe application, EPA used directly applicable monitoring data, which is in the highest of the approach hierarchy, including data from 4 sources. These data have data quality ratings ranging from medium to high.

Primary Limitations

EPA did not find exposure duration data and assumed a high-end of 8 hours based on the length of a full shift and a central tendency of 4 hours based on the mid-range of a shift. The representativeness of the assumed estimates of duration of inhalation and dermal exposure for the assessed cleaning activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with minimal to no employee training or no glove usage due to the wide-spread use of cleaning products. The assumed glove protection factor values are uncertain.

The worker activities associated with the monitoring data used to assess inhalation exposure during dip cleaning and spray/wipe cleaning were not detailed for all samples. Where EPA could not determine the type of cleaning activities associated with a data point, EPA used the data in the estimates for both dip and spray/wipe cleaning. For both occupational exposure scenarios, the representativeness of the monitoring data toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium.

2.4.1.2.14 Fertilizer Application

This scenario includes the use of fertilizers containing NMP. For this commercial exposure scenario, EPA assessed inhalation, vapor-through-skin, and dermal exposures to NMP during application of fertilizers.

While EPA does expect that workers may perform additional activities during this scenario, such as unloading or maintenance activities, EPA expects that fertilizer application presents the largest range of potential exposures.

Inhalation and Vapor-through-Skin

EPA did not find inhalation monitoring data for the application of fertilizers containing NMP. EPA found modeled inhalation exposures during spray and fog application of agrochemicals (RIVM, 2013). EPA uses the modeled exposures to assess potential inhalation exposures during this life cycle stage. These data have a data quality rating of high.

The input parameters used for the PBPK modeling based on the modeled exposures are summarized in Table 2-54. EPA did not model data on short-term inhalation exposures during the application of fertilizers containing. The supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r) provides additional details.

Table 2-54. Summary of Parameters for PBPK Modeling of Worker Inhalation Exposure During Fertilizer Application

Work Activity	Parameter Characterization	Full-Shift NMP Air Concentration (mg/m^3, 8-hr TWA)	Duration-Based NMP Air Concentration (mg/m^3)	Source	Data Quality Rating
Manual spray or boom application of fertilizers	Central tendency (unknown statistical characterization)	2.97	No data	(RIVM, 2013)	High
	High-end (unknown statistical characterization)	5.27	No data		

Dermal

Table 2-55 summarizes the parameters used to assess dermal exposure during the use of agricultural products containing NMP. Most of these parameters were determined based on assumptions described in Section 2.4.1.1. EPA used data from literature, public comments, and the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017) to determine the NMP weight fraction. The underlying data have a data quality rating of high. Because this scenario covers a variety of commercial and industrial sites, EPA assumes that either no gloves are used or, if gloves are used, there is no permeation data to indicate the glove material is protective for NMP, corresponding to a protection factor of 1. EPA assesses a central tendency scenario assuming the use of gloves with minimal to no employee training, due to the widespread nature of this occupational exposure scenario, corresponding to a protection factor of 5.

Table 2-55. Summary of Parameters for Worker Dermal Exposure During Fertilizer Application

Work Activity	Parameter Characterization	Glove Protection Factor(s)	NMP Weight Fraction	Skin Surface Area Exposed [a]	Exposure Duration	Body Weight [a]
			Unitless	cm^2	hr/day	kg
Manual spray or boom application of fertilizers	Central Tendency	5	0.001	445 (f) 535 (m)	4	74 (f) 88 (m)
	High-End	1	0.07	890 (f) 1,070 (m)	8	

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

PBPK Inputs

EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-56.

The numeric parameters corresponding to the characterizations presented in Table 2-56 are summarized in Table 2-57. These are the inputs used in the PBPK model.

Table 2-56. Characterization of PBPK Model Input Parameters for Fertilizer Application

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	Manual spray or boom application	Central tendency (unknown statistical characterization)	Calculated 4-hr TWA from the 8-hr TWA data	1-hand	Yes	Central Tendency
High-end	Manual spray or boom application	High-end (unknown statistical characterization)	Based on 8-hr TWA data	2-hand	No	High-end

Table 2-57. PBPK Model Input Parameters for Fertilizer Application

Scenario	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Central Tendency	5.94	4	445 (f) 535 (m)	5	0.001	74 (f) 88 (m)
High-end	5.27	8	890 (f) 1,070 (m)	1	0.07	74 (f) 88 (m)

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed to liquid NMP of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Summary

In summary, dermal and inhalation exposures are expected for this use. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

EPA assessed dermal exposure to 0.1 to 7% NMP, based on data from public comments and literature, which have data quality ratings of high. EPA assessed occupational inhalation exposure during fertilizer application using a modeled inhalation exposure concentration value, which is in the middle of the approach hierarchy, from RIVM (2013). This data has a data quality rating of high.

Primary Limitations

EPA did not find exposure duration data and assumed a high-end of 8 hours based on the length of a full shift and a central tendency of 4 hours based on the mid-range of a shift. The representativeness of the assumed estimates of duration of inhalation and dermal exposure toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with minimal to no employee training or no glove usage due to the commercial nature of this use. The assumed glove protection factor values are uncertain. The modeled inhalation exposure concentration was obtained from RIVM (2013) and not generated by EPA. The representativeness of the modeled exposure toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium.

2.4.1.2.15 Wood Preservatives

This scenario includes the use of wood preservatives containing NMP. For this commercial exposure scenario, EPA assessed inhalation, vapor-through-skin, and dermal exposures to NMP during brush application of these wood preservatives. EPA does not expect other application methods because the identified wood preservative production containing NMP is a paste.

Based on the process description, EPA expects that workers apply the paste wood preservative directly from its container using a scraper. EPA does not expect unloading activities or the use of equipment requiring maintenance or cleaning. EPA expects the actual application of wood preservatives presents the largest range of potential exposures.

Inhalation and Vapor-through-Skin

EPA compiled air concentration monitoring data and modeled data for NMP-based wood preservative application from published literature sources. Due to limited relevance and quality of monitoring data and modeling estimates for solvents used in the application of wood preservatives found in the published literature, EPA used modeling estimates with the highest data quality for this use.

The modeled exposure from brush application is summarized into the input parameters used for the PBPK modeling in Table 2-58. EPA did not find data on short-term exposures for this life cycle stage. The supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r) provides additional details.

Table 2-58. Summary of Parameters for Wood Preservatives

Work Activity	Parameter Characterization	Full-Shift NMP Air Concentration (mg/m^3, 8-hr TWA)	Duration-Based NMP Air Concentration (mg/m^3)	Source	Data Quality Rating
Brush Application	Single Estimate	4.13	No data	(RIVM, 2013)	High

Dermal

Table 2-59 summarizes the parameters used to assess dermal exposure during the use of wood preservatives containing NMP. Most of these parameters were determined based on assumptions described in Section 2.4.1.1. EPA used data from the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017) to determine the NMP weight fraction. Because this scenario covers a variety of commercial and industrial sites, EPA assumes that either no gloves are used or, if gloves are used, there is no permeation data to indicate the glove material is protective for NMP, corresponding to a protection factor of 1. EPA assesses a central tendency scenario assuming the use of gloves with minimal to no employee training, corresponding to a protection factor of 5.

Table 2-59. Summary of Parameters for Worker Dermal Exposure to Wood Preservatives

Work Activity	Parameter Characterization	Glove Protection Factor(s)	NMP Weight Fraction	Skin Surface Area Exposed [a]	Exposure Duration	Body Weight [a]
			Unitless	cm^2	hr/day	kg
Brush Application	Central Tendency	5	0.01	445 (f) 535 (m)	4	74 (f) 88 (m)
	High-End	1	0.01	890 (f) 1,070 (m)	8	

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

PBPK Inputs

EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-60. The numeric parameters corresponding to the characterizations presented in Table 2-60 are summarized in Table 2-61. These are the inputs used in the PBPK model.

Table 2-60. Characterization of PBPK Model Input Parameters for Wood Preservatives

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	Brush application	Single Estimate	Assumed 4 hours	1-hand	Yes	Single data point available and used for both exposure scenarios
High-end	Brush application	Single Estimate	Assumed 8 hours	2-hand	No	Single data point available and used for both exposure scenarios

Table 2-61. PBPK Model Input Parameters for Wood Preservatives

Scenario	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Central Tendency	8.26	4	445 (f) 535 (m)	5	0.01	74 (f) 88 (m)
High-end	4.13	8	890 (f) 1,070 (m)	1	0.01	74 (f) 88 (m)

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Summary

In summary, dermal and inhalation exposures are expected for this use. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

EPA assessed dermal exposure to 1% NMP, based on one wood preservative product identified in the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017). EPA assessed occupational inhalation exposure during wood preservative application using a modeled inhalation exposure concentration value, which is in the middle of the approach hierarchy, from RIVM (2013). This data has a data quality rating of high.

Primary Limitations

EPA did not find exposure duration data and assumed a high-end of 8 hours based on the length of a full shift and a central tendency of 4 hours based on the mid-range of a shift. The representativeness of the assumed estimates of duration of inhalation and dermal exposure toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with minimal to no employee training or no glove usage due to the commercial nature of this use. The assumed glove protection factor values are uncertain. The modeled inhalation exposure concentration was obtained from RIVM (2013) and not generated by EPA. The representativeness of the modeled exposure toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium.

2.4.1.2.16 Recycling and Disposal

For this industrial and commercial exposure scenario, EPA assessed inhalation, vapor-through-skin, and dermal exposures from the unloading of various containers (i.e., drums, tank trucks, rail cars) containing waste NMP. While EPA does expect that workers may perform additional activities during this scenario, such as sampling or maintenance work, EPA expects that unloading activities present the largest range of potential exposures.

Inhalation and Vapor-through-Skin

EPA did not find monitoring data on the handling of NMP wastes at disposal and recycling sites. EPA therefore compiled the same monitoring and modeled exposure concentration data for this life cycle stage as that for manufacturing. As described for Manufacturing in Section 2.4.1.2.1, due to limited relevance and quality of monitoring data and modeling estimates found in the published literature, EPA used modeling estimates with the highest data quality for this use, as further described below. The *Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model* involves deterministic modeling and the *Drum Loading and Unloading Release and Inhalation Exposure Model* involves probabilistic modeling.

The inhalation exposure concentrations modeled by EPA for unloading of NMP are summarized into the input parameters used for the PBPK modeling in Table 2-62. The modeled exposure concentrations are the same as those for Manufacturing and Repackaging; however, the exposure durations are different because they are based on the NMP volume unloaded for the exposure scenario. Note that the exposure duration for the central tendency and high-end exposure scenarios are the same for unloading drums because the unloading rate does not vary in that model. The supplemental document *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r) provides additional details.

Table 2-62. Summary of Parameters for PBPK Modeling of Worker Inhalation Exposure During Recycling and Disposal

Work Activity	Parameter Characterization	Full-Shift NMP Air Concentration (mg/m^3, 8-hr TWA)	Duration-Based NMP Air Concentration (mg/m^3)	Source	Data Quality Rating
Unloading bulk containers	Central tendency (50th percentile)	0.048	0.760 (duration = 0.5 hr)	*Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model* (U.S. EPA, 2013a)	Not applicable[a]
	High-end (95th percentile)	0.190	1.52 (duration = 1 hr)		
Unloading drums	Central tendency (50th percentile)	0.124	1.65 (duration = 0.603 hr)	*Drum Loading and Unloading Release and Inhalation Exposure Model* (U.S. EPA, 2013a)	Not applicable[a]
	High-end (95th percentile)	0.441	5.85 (duration = 0.603 hr)		

[a] EPA models are standard sources used by EPA for occupational exposure assessments. EPA did not systematically review models that were developed by EPA.

Dermal

Table 2-63 summarizes the parameters used to assess dermal exposure during worker handling of wastes containing NMP. Most parameters were determined based on assumptions described in Section 2.4.1.1. The data submitted by SIA for the use of NMP in the production of semiconductors (discussed in Section 2.4.1.2.8) include one inhalation monitoring data point for the loading of trucks with waste NMP. This data point indicates that NMP is 92% in the handled waste material (SIA, 2019). EPA uses this concentration for the central tendency NMP weight fraction. Due to lack of additional information on the concentration of NMP in waste solvents, for the high-end value, EPA assumes that waste NMP may contain very little impurities and be up to 100 weight percent NMP (e.g., residues of pure NMP in shipping containers that have been unloaded and sent without cleaning for reclamation or disposal). For this scenario, EPA assesses both high-end and central tendency scenarios assuming the use of gloves with basic employee training, corresponding to a protection factor of 10.

Table 2-63. Summary of Parameters for Worker Dermal Exposure During Recycling and Disposal

Work Activity	Parameter Characterization	Glove Protection Factor(s)	NMP Weight Fraction	Skin Surface Area Exposed [a]	Exposure Duration	Body Weight [a]
			Unitless	cm^2	hr/day	kg
Unloading bulk containers; Unloading drums	Central Tendency	10	0.92	445 (f) 535 (m)	4	74 (f) 88 (m)
	High-end	10	1	890 (f) 1,070 (m)	8	

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

PBPK Inputs

EPA assessed PBPK parameters for central tendency and high-end exposure scenarios based on the characterizations listed in Table 2-64. The numeric parameters corresponding to the characterizations presented in Table 2-64 are summarized in Table 2-65. These are the inputs used in the PBPK model.

Table 2-64. Characterization of PBPK Model Input Parameters for Recycle and Disposal

Scenario	Work Activity	Air Concentration Data Characterization	Exposure Duration	Skin Surface Area Exposed	Gloves	NMP Weight Fraction Characterization
Central Tendency	Unloading bulk containers	Central tendency (50^{th} percentile)	Duration calculated by model	1-hand	Yes	Central tendency
High-end	Unloading drums	High-end (95^{th} percentile)	Duration calculated by model	2-hand	Yes	High-end

Table 2-65. PBPK Model Input Parameters for Recycle and Disposal

Scenario	Duration-Based NMP Air Concentration (mg/m^3)	Exposure Duration (hr)	Skin Surface Area Exposed (cm^2) [a,b]	Gloves Protection Factor	NMP Weight Fraction	Body Weight (kg) [a]
Central Tendency	0.760	0.5	445 (f) 535 (m)	10	0.92	74 (f) 88 (m)
High-end	5.85	0.603	890 (f) 1,070 (m)	10	1	74 (f) 88 (m)

[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).
[b] EPA assessed a skin surface area exposed to liquid NMP of 0.1 cm^2 for ONUs for each scenario. However, EPA did not assess glove usage (protection factor = 1) for ONUs.

Summary

In summary, dermal and inhalation exposures are expected for this use. EPA has not identified additional uncertainties for this use beyond those included in Section 2.4.1.4. EPA identified primary strengths and limitations and assigned an overall confidence to the occupational exposure scenario inputs to the PBPK model, as discussed below. EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence. Note that the effects of the limitations on this assessment are discussed in Section 2.4.1.4.

Primary Strengths

Modeling, in the middle of the approach hierarchy, was used to estimate occupational inhalation exposure concentrations for both the unloading of NMP from bulk containers and from drums. For modeling of these air concentrations, EPA attempted to address variability in input parameters by estimating both central tendency and high-end parameter values. Additionally, for modeling of air concentrations during the unloading of drums, EPA used Monte Carlo simulation to capture variability in input parameters. EPA expects the duration of inhalation and dermal exposure to be realistic for the unloading activities, as the durations are based on the length of time to unload NMP from specific container sizes (i.e., tank trucks, rail cars, and drums).

Primary Limitations

The representativeness of the estimates of duration of inhalation and dermal exposure for the unloading activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. EPA did not find NMP concentration data and assumed waste NMP may contain very little impurities and be up to 100% NMP. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with basic employee training is likely based on professional judgment. The assumed glove protection factor values are uncertain. For the modeling of NMP air concentrations, EPA is uncertain of the accuracy of the emission factors used to estimate fugitive NMP emissions and thereby estimate worker inhalation exposure concentration. The representativeness of the modeling results toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium.

2.4.1.3 Summary of Occupational Exposure Assessment

Table 2-66 shows the occupational dermal and inhalation exposure parameters used in the PBPK modeling for this assessment. The skin surface area and body weight dermal parameters were specific to PESS of interest: males, pregnant women, and women of childbearing age who may become pregnant. For each Occupational Exposure Scenario, a central scenario and a higher-end scenario are provided. Table 2-67 shows the results of the PBPK modeling.

For high-end scenarios where glove use was assumed and MOEs were above the benchmark MOE, EPA conducted additional modeling of exposures for no glove use to determine whether lack of glove use could result in MOEs below the benchmark MOE. The results of this additional modeling are shown in Section 4.2.2.

Table 2-66. Parameter Inputs to PBPK for Central and High-End Scenarios by Use

Use Scenario	Scenario Characterization	Sub-scenario	Weight Fraction in formulation	Surf Area exposed to liquid (cm^2) [a]	Exposure duration (hr)	Duration-based Air Conc (mg/m^3)	Gloves Protection Factor
Section 2.4.1.2.1 Manufacturing	Central tendency	Bulk container loading	1	445 (f) 535 (m)	0.5	0.76	10
	High-end	Drum loading	1	890 (f) 1,070 (m)	2.06	5.85	10
Section 2.4.1.2.2 Repackaging	Central tendency	Bulk container unloading	1	445 (f) 535 (m)	0.5	0.76	10
	High-end	Drum unloading	1	890 (f) 1,070 (m)	2.06	5.85	10
Section 2.4.1.2.3 Chemical Processing, Excluding Formulation	Central tendency	Drum unloading	1	445 (f) 535 (m)	0.36	1.65	10
	High-end	Drum unloading	1	890 (f) 1,070 (m)	0.36	5.85	10
Section 2.4.1.2.4 Incorporation into Formulation, Mixture, or Reaction Product	Central tendency	Drum unloading	1	445 (f) 535 (m)	0.36	1.65	10
	High-end	Maintenance, bottling, shipping, loading	1	890 (f) 1,070 (m)	8	12.8	10
Section 2.4.1.2.5 Metal Finishing	Central tendency	Spray application	0.6	445 (f) 535 (m)	4	0.53	5
	High-end	Spray application	0.9	890 (f) 1,070 (m)	8	4.51	1
	Central tendency	Dip application	0.6	445 (f) 535 (m)	4	1.98	5
	High-end	Dip application	0.9	890 (f) 1,070 (m)	8	2.75	1
	Central tendency	Brush application	0.6	445 (f) 535 (m)	4	8.26	5
	High-end	Brush application	0.9	890 (f) 1,070 (m)	8	4.13	1
Section 2.4.1.2.6 Removal of Paints, Coatings, Adhesives and Sealants	Central tendency	Miscellaneous removal	0.305	445 (f) 535 (m)	1	13.2	5
	High-end	Miscellaneous removal	0.695	890 (f) 1,070 (m)	8	64	1
	Central tendency	Graffiti removal	0.5	445 (f) 535 (m)	4	2.02	5
	High-end	Graffiti removal	0.613	890 (f)	8	4.52	1

Use Scenario	Scenario Characterization	Sub-scenario	Weight Fraction in formulation	Surf Area exposed to liquid (cm^2) [a]	Exposure duration (hr)	Duration-based Air Conc (mg/m^3)	Gloves Protection Factor
				1,070 (m)			
Section 2.4.1.2.7 Application of Paints, Coatings, Adhesives and Sealants	Central tendency	Spray application	0.02	445 (f) 535 (m)	4	0.53	5
	High-end	Spray application	0.534	890 (f) 1,070 (m)	8	4.51	1
	Central tendency	Roll/curtain application	0.02	445 (f) 535 (m)	4	0.06	5
	High-end	Roll/curtain application	0.534	890 (f) 1,070 (m)	8	0.19	1
	Central tendency	Dip application	0.02	445 (f) 535 (m)	4	1.98	5
	High-end	Dip application	0.534	890 (f) 1,070 (m)	8	2.75	1
	Central tendency	Brush application	0.02	445 (f) 535 (m)	4	8.26	5
	High-end	Brush application	0.534	890 (f) 1,070 (m)	8	4.13	1
Section 2.4.1.2.8 Electronic Parts Manufacturing	Central tendency	Container handling, small containers	0.60	445 (f) 535 (m)	6	1.01	10
	High-end	Container handling, small containers	0.75	890 (f) 1,070 (m)	12	0.608	10
	Central tendency	Container handling, drums	0.5	445 (f) 535 (m)	6	0.026	10
	High-end	Container handling, drums	0.75	890 (f) 1,070 (m)	12	1.54	10
	Central tendency	Fab worker	0.15	445 (f) 535 (m)	6	0.276	10
	High-end	Fab worker	0.999	890 (f) 1,070 (m)	12	0.405	10
	Central tendency	Maintenance	0.55	445 (f) 535 (m)	6	0.040	10
	High-end	Maintenance	1	890 (f) 1,070 (m)	12	0.690	10
	Central tendency	Virgin NMP truck unloading	1	445 (f) 535 (m)	4	9.56	10
	High-end	Virgin NMP truck unloading	1	890 (f) 1,070 (m)	8	4.78	10

Use Scenario	Scenario Characterization	Sub-scenario	Weight Fraction in formulation	Surf Area exposed to liquid (cm^2) [a]	Exposure duration (hr)	Duration-based Air Conc (mg/m^3)	Gloves Protection Factor
	Central tendency	Waste truck loading	0.92	445 (f) 535 (m)	4	1.42	10
	High-end	Waste truck loading	0.95	890 (f) 1,070 (m)	8	0.709	10
Section 2.4.1.2.9 Printing and Writing	Central tendency	Printing	0.05	445 (f) 535 (m)	4	0.016	5
	High-end	Printing	0.07	890 (f) 1,070 (m)	8	0.172	1
	Central tendency	Writing	0.1	1	0.5	0	5
	High-end	Writing	0.2	1	0.5	0	1
Section 2.4.1.2.10 Soldering	Central tendency	Soldering	0.01	445 (f) 535 (m)	4	0	5
	High-end	Soldering	0.025	890 (f) 1,070 (m)	8	0	1
Section 2.4.1.2.11 Commercial Automotive Servicing	Central tendency	Aerosol Degreasing	0.025	445 (f) 535 (m)	1	19.96	5
	High-end	Aerosol Degreasing	0.33	890 (f) 1,070 (m)	8	43.4	1
Section 2.4.1.2.12 Laboratory Use	Central tendency	Laboratory use	1	445 (f) 535 (m)	2	0.200	10
	High-end	Laboratory use	1	890 (f) 1,070 (m)	8	4.13	10
Section 2.4.1.2.13 Cleaning	Central tendency	Dip Cleaning	0.845	445 (f) 535 (m)	4	1.98	5
	High-end	Dip Cleaning	0.999	890 (f) 1,070 (m)	8	2.75	1
	Central tendency	Spray / Wipe Cleaning	0.313	445 (f) 535 (m)	4	2.02	5
	High-end	Spray / Wipe Cleaning	0.989	890 (f) 1,070 (m)	8	3.38	1
Section 2.4.1.2.14 Fertilizer Application	Central tendency	Manual spray or boom application	0.001	445 (f) 535 (m)	4	5.94	5
	High-end	Manual spray or boom application	0.07	890 (f) 1,070 (m)	8	5.27	1
Section 2.4.1.2.15 Wood Preservatives	Central tendency	Brush application	0.01	445 (f) 535 (m)	4	8.26	5
	High-end	Brush application	0.01	890 (f) 1,070 (m)	8	4.13	1

Use Scenario	Scenario Characterization	Sub-scenario	Weight Fraction in formulation	Surf Area exposed to liquid (cm^2) [a]	Exposure duration (hr)	Duration-based Air Conc (mg/m^3)	Gloves Protection Factor
Section 2.4.1.2.16 Recycling and Disposal	Central tendency	Bulk container unloading	0.92	445 (f) 535 (m)	0.5	0.760	10
	High-end	Drum unloading	1	890 (f) 1,070 (m)	0.603	5.85	10

Note: The prevalence of respirator use is not known but may be unlikely for most scenarios. Some "what-if" scenarios were generated assuming the use of APF 10 respirators. These scenarios are shown in Section 4.2.2.
[a] EPA assessed these exposure factors for both females and males. Values associated with females are denoted with (f) and values associated with males are denoted with (m).

Table 2-67. PBPK Exposure Results for Central and High-End Worker and ONU Scenarios by Use

Use Scenario	Scenario Characterization	Sub-scenario	Acute Exposure, Peak blood concentration (mg/L) (female)	Chronic Exposure, AUC (hr mg/L) (male)	Chronic Exposure, AUC (hr mg/L) (ONU)
Section 2.4.1.2.1 Manufacturing	Central tendency	Bulk container loading	0.42	0.86	0.011
	High-end	Drum loading	2.14	7.4	0.31
Section 2.4.1.2.2 Repackaging	Central tendency	Bulk container unloading	0.42	0.86	0.011
	High-end	Drum unloading	2.14	7.4	0.31
Section 2.4.1.2.3 Chemical Processing, Excluding Formulation	Central tendency	Drum unloading	0.35	0.63	0.016
	High-end	Drum unloading	0.72	1.3	0.055
Section 2.4.1.2.4 Incorporation into Formulation, Mixture, or Reaction Product	Central tendency	Drum unloading	0.35	0.63	0.016
	High-end	Maintenance, bottling, shipping, loading	4.39	30.9	2.63
Section 2.4.1.2.5 Metal Finishing	Central tendency	Spray application	1.83	8.3	0.053
	High-end	Spray application	46.3	347	0.94
	Central tendency	Dip application	1.87	8.5	0.20
	High-end	Dip application	46.2	346	0.58
	Central tendency	Brush application	2.01	9.1	0.81
	High-end	Brush application	46.3	347	0.86

Use Scenario	Scenario Characterization	Sub-scenario	Acute Exposure, Peak blood concentration (mg/L) (female)	Chronic Exposure, AUC (hr mg/L) (male)	Chronic Exposure, AUC (hr mg/L) (ONU)
Section 2.4.1.2.6 Removal of Paints, Coatings, Adhesives and Sealants	Central tendency	Miscellaneous removal	0.51	1.4	0.32
	High-end	Miscellaneous removal	36.5	268	13
	Central tendency	Graffiti removal	1.56	7.1	0.20
	High-end	Graffiti removal	29.2	212	0.93
Section 2.4.1.2.7 Application of Paints, Coatings, Adhesives and Sealants	Central tendency	Spray application	0.07	0.32	0.052
	High-end	Spray application	24.9	179.6	0.93
	Central tendency	Roll/curtain application	0.06	0.28	0.0059
	High-end	Roll/curtain application	24.7	178.4	0.052
	Central tendency	Dip application	0.10	0.47	0.19
	High-end	Dip application	24.8	179.1	0.57
	Central tendency	Brush application	0.25	1.08	0.81
	High-end	Brush application	24.8	179.5	0.85
Section 2.4.1.2.8 Electronic Parts Manufacturing	Central tendency	Container handling, small containers	1.1	6.31	0.15
	High-end	Container handling, small containers	3.3	31.8	0.21
	Central tendency	Container handling, drums	0.86	5.13	0.0043
	High-end	Container handling, drums	3.4	32.1	0.50
	Central tendency	Fab worker	0.26	1.57	0.041
	High-end	Fab worker	4.5	42.8	0.16
	Central tendency	Maintenance	0.95	5.65	0.0064
	High-end	Maintenance	4.5	42.9	0.25
	Central tendency	Virgin NMP truck unloading	1.7	7.83	0.94
	High-end	Virgin NMP truck unloading	4.1	29.2	0.99
	Central tendency	Waste truck loading	1.4	6.45	0.14
	High-end	Waste truck loading	3.7	26.0	0.17
Section 2.4.1.2.9 Printing and Writing	Central tendency	Printing	0.15	0.68	0.0017
	High-end	Printing	2.8	19.5	0.037
	Central tendency	Writing	0.00019	0.00032	0.000032
	High-end	Writing	0.0019	0.0032	0.00032
Section 2.4.1.2.10 Soldering	Central tendency	Soldering	0.03	0.14	0.000025
	High-end	Soldering	0.97	6.8	0.00063
Section 2.4.1.2.11 Commercial	Central tendency	Aerosol Degreasing	0.21	0.6	0.49
	High-end	Aerosol Degreasing	15.9	113	8.91

Use Scenario	Scenario Characterization	Sub-scenario	Acute Exposure, Peak blood concentration (mg/L) (female)	Chronic Exposure, AUC (hr mg/L) (male)	Chronic Exposure, AUC (hr mg/L) (ONU)
Automotive Servicing					
Section 2.4.1.2.12 Laboratory Use	Central tendency	Laboratory use	1.0	3.4	0.010
	High-end	Laboratory use	4.1	29	0.81
Section 2.4.1.2.13 Cleaning	Central tendency	Dip Cleaning	2.62	12	0.20
	High-end	Dip Cleaning	52.6	399	0.58
	Central tendency	Spray / Wipe Cleaning	0.99	4.5	0.20
	High-end	Spray / Wipe Cleaning	52.0	393	0.71
Section 2.4.1.2.14 Fertilizer Application	Central tendency	Manual spray or boom application	0.14	0.60	0.58
	High-end	Manual spray or boom application	2.9	20.6	1.1
Section 2.4.1.2.15 Wood Preservatives	Central tendency	Brush application	0.22	0.95	0.81
	High-end	Brush application	0.51	3.5	0.84
Section 2.4.1.2.16 Recycling and Disposal	Central tendency	Bulk container unloading	0.38	0.79	0.011
	High-end	Drum unloading	0.96	2.14	0.091

2.4.1.4 Summary of Uncertainties for Occupational Exposure Parameters

Key uncertainties in the occupational exposure parameters are summarized below. Most parameters are related specifically to the route of dermal contact with liquids by workers, while air concentrations are related to the routes of inhalation and vapor-through-skin exposure. The body weight parameter is related to all of these routes. The assumed values for human body weight have relatively lower uncertainties, and the median values used may underestimate exposures at the high-end of PBPK exposure results.

Dermal Exposure Parameters

The dermal exposure parameters used in this assessment have uncertainties because many parameters lack data and were therefore based on assumptions. The assumed parameter values with the greatest uncertainties are glove use and effectiveness (using protection factors based on the ECETOC TRA model that are what-if type values as described in Section 2.4.1.1), durations of contact with liquid, and skin surface areas for contact with liquids. The assumed values for effectiveness, durations of contact, and surface areas for contact may or may not be representative of actual values. The assumed values for NMP concentrations in formulations have relatively lower uncertainties. The midpoints of some ranges serve as substitutes for 50th percentiles of the actual distributions and high ends of ranges serve as substitutes for 95th percentiles of the actual distributions. However, these substitutes are uncertain and

are weak substitutes for the ideal percentile values. Generally, EPA cannot determine whether most of these assumptions may overestimate or underestimate exposures. However, high-end duration of dermal contact estimates of 8 hours may be more likely to overestimate exposure potential to some extent, and some activity-based durations may be more likely to underestimate exposure potential to some extent. For many OESs, the high-end surface area assumption of contact over the full area of two hands likely overestimates exposures. Occupational non-users (ONUs) may have direct contact with NMP-based liquid products due to incidental exposure at shared work areas with workers who directly work with NMP, and the estimate of zero surface area contact may underestimate their exposure. The parameter values NMP concentrations are from available data and are likely to have a relatively low impact on the magnitude (less than an order of magnitude, or factor of 10) of overestimation or underestimation of exposure. The impact of vapors being trapped next to the skin during glove use is also uncertain.

Inhalation and Vapor-through-Skin Exposure Parameters

Where monitoring data are available, limitations of the data also introduce uncertainties into the exposures. The principal limitation of the air concentration data is the uncertainty in the representativeness of the data. EPA identified a limited number of exposure studies and data sets that provided data for facilities or job sites where NMP was used. Some of these studies primarily focused on single sites. This small sample pool introduces uncertainty as it is unclear how representative the data for a specific end use are for all sites and all workers across the US. Differences in work practices and engineering controls across sites can introduce variability and limit the representativeness of any one site relative to all sites. Age of the monitoring data can also introduce uncertainty due to differences in work practices and equipment used at the time the monitoring data were taken and those used currently, so the use of older data may over- or underestimate exposures. Additionally, some data sources may be inherently biased. For example, bias may be present if exposure monitoring was conducted to address concerns regarding adverse human health effects reported following exposures during use. The effects of these uncertainties on the occupational exposure assessment are unknown, as the uncertainties may result in either over or underestimation of exposures depending on the actual distribution of inhalation exposure concentrations and the variability of work practices among different sites.

The impact of these uncertainties precluded EPA from describing actual parameter distributions. In most scenarios where data were available, EPA did not find enough data to determine complete statistical distributions. Ideally, EPA would like to know 50th and 95th percentiles for each exposed population. In the absence of percentile data for monitoring, the means or midpoint of the range serve as substitutes for 50th percentiles of the actual distributions and high ends of ranges serve as substitutes for 95th percentiles of the actual distributions. However, these substitutes are uncertain and are weak substitutes for the ideal percentile values. The effects of these substitutes on the occupational exposure assessment are unknown, as the substitutes may result in either over or underestimation of exposures depending on the actual distribution.

Where data were not available, the modeling approaches used to estimate air concentrations also have uncertainties. Parameter values used in models did not all have distributions known to represent the modeled scenario. It is also uncertain whether the model equations generate results that represent actual workplace air concentrations. Some activity-based modeling does not account for exposures from other activities, which may result in underestimates of exposures. When EPA does not have ONU-specific exposure data, EPA's assumption that 50th percentile air concentrations predicted for workers in these activities are a good approximation of exposure is uncertain. It is not known whether this assumption

underestimates or overestimates exposure for ONUs. Additional model-specific uncertainties are included below. In general, unless specified otherwise, the effects of the below model-specific uncertainties on the exposure estimates are unknown, as the uncertainties may result in either over or underestimation on exposures depending on the actual distributions of each of the model input parameters.

Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model
For manufacturing; repackaging; and recycling and disposal, the *Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model* was used to estimate the airborne concentration associated with generic chemical loading scenarios at industrial facilities. Specific uncertainties associated with this model are described below:

- After each loading event, the model assumes saturated air containing NMP that remains in the transfer hose and/or loading arm is released to air. The model calculates the quantity of saturated air using design dimensions of loading systems published in the OPW Engineered Systems catalog and engineering professional judgment. These dimensions may not be representative of the whole range of loading equipment used at industrial facilities handling NMP.
- The model estimates fugitive emissions from equipment leaks using total organic compound emission factors from EPA's *Protocol for Equipment Leak Emission Estimates* (U.S. EPA, 1995), and professional judgment on the likely equipment type used for transfer (e.g. number of valves, seals, lines, and connections). The applicability of these emission factors to NMP, and the accuracy of EPA's assumption on equipment type are not known.

Drum Loading and Unloading Release and Inhalation Exposure Model
For chemical processing, excluding formulation and incorporation into formulation, mixture, or reaction product, the *Drum Loading and Unloading Release and Inhalation Exposure Model* was used to estimate the airborne concentration associated with generic chemical loading scenarios at industrial facilities. Specific uncertainties associated with this model are described below:

- The model estimates fugitive emissions using the *EPA/OAQPS AP-42 Loading Model.* The applicability of the emission factors used in this model to NMP is not known.
- EPA assigned statistical distributions based on available literature data or professional judgment to address the variability in Ventilation Rate (Q), Mixing Factor (k), Vapor Saturation Factor (f), and Exposed Working Years per Lifetime (WY). The selected distributions may vary from the actual distributions.

Model for Occupational Exposures during Aerosol Degreasing of Automotive Brakes
The aerosol degreasing assessment uses a near-field/far-field approach (uncertainties on this approach are presented below) to model worker exposure. Specific uncertainties associated with the aerosol degreasing scenario are presented below:

- The model references a CARB study (CARB, 2000) on brake servicing to estimate use rate and application frequency of the degreasing product. The brake servicing scenario may not be representative of the use rates for other aerosol degreasing applications involving NMP;
- Aerosol formulations were taken from available safety data sheets, and some were provided as ranges. For each Monte Carlo iteration the model selects an NMP concentration within the range

of concentrations using a uniform distribution. In reality, the NMP concentration in the formulation may be more consistent than the range provided.

Near-Field/Far-Field Model Framework

The near-field/far-field approach is used as a framework to model inhalation exposure for aerosol degreasing. The following describe uncertainties and simplifying assumptions generally associated with this modeling approach:

- There is some degree of uncertainty associated with each model input parameter. In general, the model inputs were determined based on review of available literature. Where the distribution of the input parameter is known, a distribution is assigned to capture uncertainty in the Monte Carlo analysis. Where the distribution is unknown, a uniform distribution is often used. The use of a uniform distribution will capture the low-end and high-end values but may not accurately reflect actual distribution of the input parameters.
- The model assumes the near-field and far-field are well mixed, such that each zone can be approximated by a single, average concentration.
- All emissions from the facility are assumed to enter the near-field. This assumption will overestimate exposures and risks in facilities where some emissions do not enter the airspaces relevant to worker exposure modeling.
- The exposure models estimate airborne concentrations. Exposures are calculated by assuming workers spend the entire activity duration in their respective exposure zones (i.e., the worker in the near-field and the occupational non-user in the far-field). A worker may walk away from the near-field during part of the process. As such, assuming the worker is exposed at the near-field concentration for the entire activity duration may overestimate exposure.
- The exposure models represent model workplace settings for NMP used in aerosol degreasing of automotive brakes. The model has not been regressed or fitted with monitoring data.

2.4.2 Consumer Exposures

NMP is found in consumer products that are available for purchase at retail stores or via the internet (Abt, 2017). Use of these products can result in consumer exposures. As presented in the previous 2015 EPA NMP Paint Remover Risk Assessment, women of child-bearing age and pregnant women are the populations identified as at risk due to the hazards of NMP and exposures. That is, the hazard endpoint, identified in the Paint Remover Risk Assessment and confirmed in this Risk Evaluation affects the fetus, and could present a risk to women of child-bearing age or pregnant women (see Section 3.2 and (U.S. EPA, 2015)).

2.4.2.1 Consumer Exposures Approach and Methodology

EPA selected currently available NMP-containing consumer products for exposure analysis that had uses covered under the Toxic Substances Control Act (see Table 2-68). EPA recognizes that there are numerous other products containing NMP which are not subject to TSCA, as noted in the NMP Problem Formulation. For example, NMP is found in cosmetics and pharmaceutical manufacture which are regulated by the Food and Drug Administration and in pesticides (as an inert ingredient) regulated by EPA but under the Federal Insecticide Fungicide and Rodenticide Act. EPA also confirmed in the NMP Market Profile previous uses of NMP-containing products that are no longer in use such as a component of the inner layer of aluminum aerosol or spray cans used for hairspray or air fresheners and which are

not based in EPA's professional judgement a reasonably foreseen use (EPA-HQ-OPPT-2016-0743-0070) (Abt, 2017).

Table 2-68. Conditions of Use for Consumer Products Containing NMP

Consumer Conditions of Use	Form	No. of Products Identified [a]	Range of Product NMP Weight Fractions [b] (%)
Sealants	Liquid	3	0.3 – 1.0
Adhesives	Liquid	1	85.0
Adhesives Remover	Liquid	5	1.0 – 60.0
Auto Interior Cleaner	Liquid	1	1.0 – 5.0
Auto Interior Spray Cleaner	Aerosol	1	1.0
Cleaners/ Degreasers	Liquid	8	1.0 – 100.0
Engine Cleaner/ Degreaser	Liquid	1	15.0 – 40.0
Paint	Liquid	3	1.0 – 7.0
Paint Removers	Liquid	35	25.0 – 50.0 [c]
Spray Lubricant (Mold release)	Aerosol	1	30.0 – 40.0
Stains, Varnishes	Liquid	10	1.0 – 10.0
Arts and Crafts	Liquid	2	0.1 – 1.0

[a] The number of products identified is based on the product lists in EPA's 2017 Market and Use Report and Preliminary Information on Manufacturing, Processing, Distribution, Use and Disposal: N-Methyl-2-pyrrolidone, as well as the 2016 Supplemental Consumer Exposure and Risk Estimation Technical Report for NMP in Paint and Coating Removal.
[b] Conditions of use with one value for weight fraction represent one product with a single value listed in the Manufacturer's Safety Data Sheet (MSDS). Several manufacturer's list a range of possible NMP weight fractions within a given product's MSDS.
[c] See the 2015 Paint Remover's Risk Assessment

EPA searched the National Institutes of Health (NIH) Household Products Database, various government and trade association sources for products containing NMP, company websites for product Safety Data Sheets (SDSs) and the internet in general. Lists of consumer products were compiled and are found in EPA's 2017 Market Profile (Abt, 2017). These products ranging from 0.1 to >85 weight percent NMP were categorized according to their respective condition(s) of use and were included in this draft risk evaluation.

In the absence of available emissions and monitoring data for use of consumer products containing NMP, a modeling approach was utilized to assess consumer exposure. Appropriate use scenarios corresponding to the product use were selected for exposure modeling and parameterization of model inputs used consumer survey data where appropriate.

The PBPK model was used to derive internal exposure estimates for consumer acute exposures. The PBPK model required a set of input parameters related to exposure by the dermal and inhalations routes:

- NMP weight fraction in the liquid product;
- Total skin surface area of hands in contact with the liquid product;
- Duration of dermal contact with the liquid product;
- Air concentration for inhalation and vapor-through-skin exposure; and

- Body weight of the exposed consumer/user.

Section 2.4.2.4 presents the input parameters in more detail. The specific PBPK model inputs and outputs are found in the NMP supplemental documents (U.S. EPA, 2019e).

EPA relied on information gathered through literature searches and data evaluation (See Section 1.5 above). In addition to product specific data from gray literature, surveys provided data needed to parameterize model inputs. Many of the model defaults are based on data from EPA's 2011 Exposure Factors Handbook (see Consumer Exposure Model guide) but were supplemented with data found from scientific literature (U.S. EPA, 2017a). For the NMP consumer exposure assessment, existing assessments such as the 2015 U.S. EPA Paint Remover Risk Assessment and other assessments as listed in Table 2-68 also provided supplementary information and data.

Table 2-69 lists some of the key sources of information evaluated under the data evaluation process and used in the consumer exposure assessment. A description of the evaluation metrics and confidence scores for each of the sources is presented in the NMP supplemental document *Risk Evaluation for N-Methylpyrrolidone, Systematic Review Supplemental File: Data Quality Evaluation of Consumer and General Population Studies* (U.S. EPA, 2019h). The one indoor air monitoring study is discussed below in Section 2.4.2.5 under consumer use of paint removers.

Table 2-69. Consumer Exposures Assessment Literature Sources

Source Reference	Data Type	Confidence Rating
(U.S. EPA, 1994a)	Survey Data	Medium (1.8)
(U.S. EPA, 1987)	Survey Data	High (1.3)
(Abt, 1992)	Survey Data	Medium (1.8)
(Danish Ministry of the Environment, 2015)	Completed Assessments	High (1.5)
(DTI, 2004)	Completed Assessments	High (1.6)
(ECHA, 2014)	Completed Assessments	High (1.0)
(Environment Canada, 2017)	Completed Assessments	High (1.5)
(Kiefer, 1994)	Monitoring	Low (2.5)

2.4.2.2 Exposure Routes

Based on reasonably available information on the toxicity profile and physicochemical properties of NMP as well as the previous NMP Paint Remover Risk Assessment, the primary routes of exposure for human health concerns are dermal, including vapor through skin, and inhalation exposures.

Oral

EPA considered the oral pathway for consumers based on children's exposure potential via mouthing articles containing NMP (WSDE, 2014). EPA reviewed several NMP assessments (see Table 2-69 above), including a Danish assessment specific to consumer product mouthing and NMP migration.

Based on an estimated NMP migration amount of 200µg, the Danish study concluded that NMP from articles such as toothbrushes do not pose a risk (DTI, 2004).
Using the Consumer Exposure Model, EPA estimated the exposure to NMP due to mouthing of fabric articles such as blankets, dolls, or stuffed animals to young children. EPA evaluated NMP exposure for 3 lifestages, infant (<1 year), infant (1-2 years), and small child (3-5 years) (see Table 2-70). Infants younger than one year would have the greatest possible exposure via mouthing, however levels of 15µg are significantly less than the migration amount reported in the Danish study and well below the oral dose of 48mg/kg/day that could result in risk. EPA did not further analyze NMP exposure via the oral pathway in this risk evaluation.

Table 2-70. NMP Oral Exposure to Children via Mouthing

Receptor	Fabric: blanket, doll, stuffed animal (weight fraction)	Mouthing Duration (min)	Body Weight (kg)	Acute Dose Rate (mg/kg/day)
Infant (<1 year)	1.0E-03	22.5	7.8	1.5E-02
Infant (1-2 years)	1.0E-03	22.5	12.6	9.2E-03
Small child (3-5 years)	1.0E-03	22.5	18.6	6.2E-03

Dermal

NMP has unique physicochemical properties such that it is very efficiently dermally absorbed. Dermal absorption was characterized for consumers as it was characterized in the previous NMP Paint Remover Risk Assessment most importantly in that consumers were assumed not to wear gloves when using NMP-containing products. For the consumer exposure evaluation, dermal absorption is an important route of NMP exposure for consumers.

NMP exposure to consumers via vapor through skin uptake was also considered for each of the scenarios. This pathway will most likely occur in the scenario where the product is spray applied.

Inhalation

For each of the product use scenarios except for paint removers, the air concentrations of NMP resulting from consumer use were modeled using EPA's Consumer Exposure Model (CEM). For paint removers, the Paint Remover Risk Assessment estimated air concentrations using the MCCEM model. This model requires NMP emission data for the specific product and use conditions which was available through the specific paint remover study (Koontz et al., 1990). The PBPK model was used to estimate aggregate dermal, vapor through skin and inhalation exposures resulting from the uses of NMP (See Section 3.2.5.5 below and U.S. EPA (2015) for details of the PBPK model).

Based on anticipated use patterns of each of the product categories by consumers in residential settings, acute exposures via the dermal and inhalation routes were the primary scenarios of interest. EPA assumed that consumer users would be females of childbearing age (>16 and older), because, in terms of hazard, they are the most sensitive subpopulation. Other individuals, adults and children alike may be exposed via inhalation as bystanders located in the same building as the user of the NMP-containing consumer product. According to the 2015 Paint Remover risk assessment as well as the supplemental analysis presented in Section 2.4.2.5, bystanders or non-users are significantly less affected than the

direct users of the product since they do not have direct dermal contact (U.S. EPA, 2015). Bystander exposure was evaluated in this risk assessment for two high-end scenarios. Since monitoring data is not available for most of the consumer product use scenarios, CEM was used to estimate air concentrations in the breathing zone of the user. These estimates were then used to predict acute inhalation exposure to NMP for the user using the PBPK modeling approaches.

2.4.2.3 Overview of Models used in Consumer Exposure Estimates

The Consumer Exposure Module (CEM) was selected for the consumer exposure modeling as the most appropriate model to use due to the lack of available emissions and monitoring data for NMP uses other than paint removers under consideration. Moreover, EPA did not have the input parameter data from specific NMP product chamber studies required to run more complex indoor air models for the consumer products under the scope of this assessment. Details of the CEM model and the advantages of using CEM in estimating consumer exposures to NMP are presented in Appendix F.

Modeling Dermal Exposure

Since consumers do not always wear gloves when using consumer products, EPA modeled dermal exposures for all NMP-containing products. Though CEM can estimate dermal exposures using a chemical permeability coefficient, EPA used the PBPK model to estimate the internal dose of NMP as it is absorbed through the skin both from direct contact of the liquid product and through absorption of vapor through skin. The PBPK model thus estimated the peak internal dose of NMP through combined routes of exposure: inhalation, dermal and vapor through skin and was also used to estimate exposures in the Paint Remover Risk Assessment.

2.4.2.4 Consumer Model Scenario and Input Parameters for Exposure to Specific NMP Uses

Table 2-71 describes the models and input parameters for women of child-bearing age that EPA evaluated in the NMP consumer exposure assessment. As indicated in Section 2.4.2.2, EPA assessed dermal and inhalation as the main exposure pathways.

Table 2-71. Product Use Input Parameters for CEM Modeling

Parameter	Units	Value / Description
CHEMICAL PROPERTIES		
Chemical of Interest	n/a	N-methyl-2-pyrrolidone
CAS Number	n/a	872-50-4
Vapor Pressure	torr	0.345
Molecular Weight	g/mol	99.1
Chemical Saturation Concentration in Air	mg/m^3	1840
Log Octanol-Water Partition Coefficient	n/a	0.38
Water Solubility	mg/mL	1000
Henry's Law Coefficient	atm/M	3.2E-09
Gas Phase Mass Transfer Coefficient	m/hr	CEM estimate, if applicable

Parameter	Units	Value / Description
MODEL SELECTION / SCENARIO INPUTS		
Inhalation Model	n/a	PBPK
Dermal Model	n/a	PBPK
Emission Rate	n/a	Let CEM Estimate Emission Rate
Product User (s)	n/a	Women of Childbearing age: Adults (≥21 years) and Young women/youth (Ages 16-20 years)
Activity Pattern	n/a	"Stay at home": user spends most of their time at home (i.e., includes room of use as well as indoor/outdoor user locations within a 24hr time period)
Product Use Start Time	n/a	9:00 AM
Background Concentration	mg/m^3	0
PRODUCT/ARTICLE PROPERTIES		
Frequency of Use (Acute)	events/day	Fixed at 1 event/day (CEM default)
Aerosol Fraction	-	CEM default (0.06)
Product Dilution Factor	unitless	Fixed at 1 (i.e., no dilution)
ENVIRONMENT INPUTS		
Building Volume (Residence)	m^3	492
Air Exchange Rate, Zone 1 (Residence)	hr^{-1}	CEM default
Air Exchange Rate, Zone 2 (Residence)	hr^{-1}	CEM default
Air Exchange Rate, Near-Field Boundary	hr^{-1}	CEM default (402)
Interzone Ventilation Rate	m^3/hr	CEM default
RECEPTOR EXPOSURE FACTORS		
Body Weight	kg	74 (Adult Women) and 65.9 (Women/Youth 16-20 years)
Averaging Time	yrs/lifetime	Acute: 1 day
Inhalation Rate-During Use	m^3/hr	0.67 (Adult and Youth 16-20 years)
Inhalation Rate-After Use	m^3/hr	0.635 (Adult) and 0.57 (Youth 16-20 years)
Dermal Surface Area	cm^2	445 (Adult) and 415 (Youth 16-20 years)

3118

Table 2-72. Consumer Conditions of Use and Modeling Input Parameters

Consumer Conditions of Use	Form	Selected U.S. EPA (1987) Survey Scenario [1]	Room of Use [2]	Duration of Use (min) [3,4]			Mass of Product Used (g, [oz]) [5]		
				10th	50th	95th	10th	50th	95th
Adhesives and Sealants	Liquid	Contact Cement, Super Glues, and Spray Adhesives	Bathroom/ Utility Room/ Outdoors	0.33	4.25	60	0.92 [0.03]	7.69 [0.25]	132.87 [4.32]
Adhesives Remover	Liquid	Adhesive Removers	Utility Room	3	60	480	17.85 [0.67]	213.17 [8]	1705.33 [64]
Auto Interior Cleaner	Liquid	Solvent-type Cleaning Fluids or Degreasers	Automobile	2	15	120	16.56 [0.56]	96.11 [3.25]	946.35 [32]
Auto Interior Spray Cleaner	Aerosol	Solvent-type Cleaning Fluids or Degreasers	Automobile	2	15	120	16.60 [0.56]	96.34 [3.25]	946.53 [32]
Cleaners/ Degreasers	Liquid	Solvent-type Cleaning Fluids or Degreasers	Utility Room	2	15	120	16.23 [0.56]	94.19 [3.25]	927.43 [32]
Engine Cleaner/ Degreaser	Liquid	Engine Cleaners/ Degreasers	Garage	5	15	120	73.15 [2.91]	291.60 [11.60]	1206.60 [48]
Paint	Liquid	Latex Paint	Garage	30	180	810	349.63 [10.67]	4194.24 [128]	23068.31 [704]
Paint Removers	Liquid	Paint Remover survey data from Abt, 1992	Bathroom/ Utility	--	90	396	--	540	1,944
Spray Lubricant (Mold release)	Aerosol	Other Lubricants (Non-Automotive)	Utility Room	0.08	2	30	3.40 [0.10]	18.71 [0.55]	170.05 [5.00]
Stains, Varnishes	Liquid	Stains, Varnishes, and Finishes	Living Room	10	60	360	61.07 [2.00]	366.42 [12.00]	3908.44 [128.00]
Arts and Crafts	Liquid	Latex Paint	Utility Room	30	180	810	5.44 [0.17]	65.27 [2.00]	358.98 [11.00]

[1] The U.S. EPA 1987 Survey was used to inform values used for duration of use and mass of product used. Where exact matches for conditions of use were not available, scenario selection was based on product categories that best met the description and usage patterns of the identified consumer conditions of use.
[2] The room of use was a selection within the Consumer Exposure Model to model the most likely location of the consumer product use and exposure.
[3] Duration of use is time of use per event and assumes only one use per day.
[4] Low-end durations of use reported by U.S.EPA 1987 that are less than 0.5 minutes are modeled as being equal to 0.5 minutes due to that being the minimum timestep available within the model.
[5] Mass of product used within U.S.EPA 1987 for given scenarios is reported in ounces but were converted to grams using reported densities in the product SDSs or MSDSs.

To estimate exposures to these products, numerous input parameters are required to generate a single exposure estimate. These parameters include the characteristics of the house, the behavior of the consumer and the emission rate of the chemical into the room of use. In the absence of measured values for many of the needed inputs, the CEM modeling for NMP used a combination of upper (95th) percentile, mean, and median as well as low-end (10th percentile) input parameters and assumptions in the calculation of potential exposure for consumer users. The 10th percentile, 50th percentile and 95th percentile inputs parameters were selected for three parameters that varied among users and were included in the 1987 Westat survey, that is, duration of product use, mass of product used, and weight fraction. This approach represents high-intensity use (95th percentile) in which the user uses a greater amount, higher NMP concentration product for a longer duration and a moderate intensity use (50th percentile weight fraction/duration/mass used) and produces acute inhalation estimates that are hypothetical but representative of the range of consumer product use. The general input parameters and assumptions are summarized in Table 2-71. The input values specific to each use scenario are summarized and explained more fully in Table 2-72. Based on the previous NMP Paint Remover Risk Assessment, the combinations of input parameters associated with low intensity use did not result in risk. Thus, for this evaluation, only the medium intensity and high intensity use scenarios were further analyzed. The general input parameters and assumptions are summarized in Table 2-71. The input values specific to each use scenario are summarized and explained more fully in Table 2-72.

Consumer behavior pattern parameters in CEM include the mass of product used, the duration of use and the frequency of use. Although the default values in CEM for these consumer behavior parameters are set to high end values, they were *not* used in this risk assessment. The other parameters (e.g., house volume) in CEM are set to mean or median values obtained from the literature. A combination of high end and mean or median values was utilized to produce high end acute inhalation exposure estimates, whereas a combination of mean and median values was used to produce central tendency acute inhalation exposure estimates.

To determine the appropriateness of the consumer behavior pattern parameters chosen in this risk evaluation, EPA examined the consumer categories available in the Westat (U.S. EPA, 1987) survey. The authors of the Westat (U.S. EPA, 1987) survey contacted thousands of Americans to gather information on consumer behavior patterns related to product categories that may contain halogenated solvents. The Westat (U.S. EPA, 1987) survey data aligned reasonably well with the description of the products that were used in this consumer exposure assessment. The data informed the values that EPA used for the mass of product used, and the time spent in the room of use when considering all surveyed individuals who identified as users of spray adhesives, spot removers, engine cleaners, brake cleaners or electronics cleaners.

The input parameter for house volume was taken from the Exposure Factors Handbook (2011). The room volume for aerosol spray adhesives and aerosol spot removers was calculated as a proxy utility room measuring 9 ft x 10 ft, with 8 ft ceilings (U.S. EPA, 2014). The designated room of use modeled for aerosol degreasers and cleaners (used as engine degreasers and brake cleaners) was the garage since users surveyed in the Westat (U.S. EPA, 1987) report reported use in the garage. The CEM model does not include a garage volume in its default room parameters, thus the median garage volume from a 2007 indoor air quality study (Batterman et al., 2007) of 15 homes in Michigan was used as a reasonable proxy value. The room of use for adhesives was reported in the product sheet as outdoors. Since CEM does not have an outdoors scenario, the garage was selected as the room of use but input parameters such as a high air exchange rate were modified to simulate the outdoors.

The user's body weight, inhalation rate, and inside of two hands surface area were set to adult (+21) and teen (16-20) women mean or the median values from the Exposure Factors Handbook (U.S. EPA, 2011) for the simulations used in this assessment.

The air exchange rate in the room of use does not take into consideration open windows or the use of an exhaust fan. While it is possible that some users may employ these exposure reduction techniques inside their homes, the goal of the consumer exposure assessment was to provide an acute exposure estimate for ventilation conditions representing average household air exchange rates. Moreover, residential users would not necessarily have the type of indoor exposure reduction tools/equipment (e.g., gloves, exhaust ventilation) that workers are likely to have in occupational settings. Consumers may not necessarily be as aware of potential chemical hazards as workers and would not have a standard operating procedure in place to assure that they use exposure reduction techniques each time they use a product.

In this assessment it was assumed that there was no pre-existing concentration of NMP in the home before product use began. The outdoor air was also assumed to be free of NMP, meaning that the air exchange rate described the intake of air with no pre-existing NMP contamination.

The products were assumed to be brushed on as a liquid to varying surfaces, where a thin film of the product was assumed to build up, evaporate, and contribute to the air concentration of the chemical in the room. EPA relied on modeled emission rates because data from chamber studies were not available. To generate emission rates, CEM used empirical data from studies assessing the emission rates of pure solvents (DTIC, 1981). CEM used the Chinn study as surrogate data to calculate the rate of evaporation of NMP from the surface to the air in the home.

The use of an exponentially decaying emission rate for NMP from the application surface was based on vapor pressure and molecular weight the equations using the Chinn method. The adhesive application should be well modeled by the Chinn study since it contained over 85% NMP. On the other hand, the spray cleaner product may have more components, and the interaction of these chemicals could alter the evaporation rate of NMP. This introduces uncertainty into the assessment, however EPA did not identify a better data set available to model the emission rates. Within the current exposure assessment, the 24-hr exposure was not strongly dependent on the emission rate due to the amount of time the product user spends in the room of use (see Table 2-72 for details).

2.4.2.5 Consumer Exposure Scenarios

Adhesives and Sealants

Exposure to NMP found in NMP-containing adhesive and sealant products was based on four products with associated weight fraction data. Three of the products had a range of weight fractions from 0.1 to 1% and were similar use products, sealants. One product was an adhesive to glue boards used in deck construction. The duration of use and mass of product used were based on the 1987 Westat survey data, specifically the data found under the Contact Cement, Super Glues, and Spray Adhesives scenario and are listed in Table 2-73.

The 'Glues and Adhesives (small scale)' default scenario within the Consumer Exposure Module (CEM) was chosen for conducting the modeling runs. This selection was the closest match to the liquid adhesive scenario among the default CEM exposure scenarios. The common modeling inputs required to

run CEM for all consumer single-use scenarios evaluated in this assessment are provided in Table 2-71. Table 2-71 also has a brief explanation of the source of each parameter and the justification for the parameter selection. Other scenario-specific input parameters are provided in Table 2-72.

CEM calculated air concentrations over the course of the simulation for the room of use and the rest of the house (Zone 1 and Zone 2). These concentrations were inputs to the PBPK model and used the body weights (74 kg, 65.9 kg), inside both hands surface areas (445 cm^2, 415 cm^2) and respiration rates (0.74 m^3/hr, 0.68 m^3/hr during use) for adult women (+21 years) and young women (16-20 years), respectively and both age groups are considered of child-bearing age in calculating the internal dose of NMP (cite: EPA definition of Childbearing age). Though both young and adult women scenarios were modeled and are presented in Appendix I.2, the difference in exposures were very small. Exposures to adult women are presented below as they are expected to adequately represent the women of child-bearing age who may use these consumer products.

Table 2-73 presents the results of the indoor air concentrations (ppm) for both central tendency and high end estimated exposures for the consumer use scenarios based on the 50th percentile and 95th percentile input parameters. Calculations detailing the conversion from acute dose rates to air concentrations are provided in a supplemental Excel spreadsheet file. (U.S. EPA, 2019d)

Table 2-73. Estimated[a] NMP Air Concentrations (Time Averaged Over 1 Day) Based on Residential Use of Adhesives or Sealants

Scenario Description For Product User (Women of Childbearing Age)	Duration of Use (min)	Weight Fraction (%)	Mass of Product Used (g)	Air Concentration [a]		
				Max 8 hr TWA (mg/m^3)	Max 8 hr TWA (ppm)	Max 24 hr TWA (ppm)
Sealant						
Medium Intensity Use [b]	4.25	0.77	7.69	4.30E-02	1.06E-02	3.76E-03
High Intensity Use [c]	60	0.77	132.87	6.18E-01	1.52E-01	5.56E-02
Adhesive						
Medium Intensity Use [b]	4.25	85	7.69	1.82E-01	4.48E-02	1.49E-02
High Intensity Use [c]	60	85	132.87	1.74	0.429	0.143

[a] See Appendix F for details about the model inputs and the method used to estimate air concentrations of NMP.
[b] Medium intensity use estimate based on using 50th percentile values for use patterns from Westat Survey (1987).
[c] High intensity use estimate based on using 95th percentile values for use patterns from Westat Survey, (1987).

The model output reports the peak concentration of NMP, however this air concentration was not used in the risk assessment. The peak concentration was the highest concentration among all 10-second time intervals that CEM simulated within a 24-hr period. The peak concentration may only exist in the room of use for a short duration and was not considered a good indicator of what the concentration of NMP would be for longer time periods. Thus, the peak concentration was not used in the risk assessment as it was not representative of a 24-hr exposure.

The maximum internal NMP dose (Cmax) resulting from inhalation, dermal and vapor through skin exposures to women of childbearing age consumer use of adhesive or sealant products as estimated from the PBPK model is presented in Table 2-74.

Table 2-74. Estimated NMP Exposures (Time Averaged Over 1 Day) Based on Residential Use of Adhesives or Sealants

Scenario Description For Product User	Women of Childbearing Age Cmax (mg/L)	Pregnant Women Cmax (mg/L)
Sealants		
Medium Intensity Use	0.011	0.011
High Intensity Use	0.070	0.068
Adhesives		
Medium Intensity Use	1.238	1.203
High Intensity Use	5.623	5.385

Adhesives Removers

Exposure to NMP found in NMP-containing adhesive remover products was based on five products with associated weight fraction data. Weight fractions ranged from 1% to 60% and were similar use products. The duration of use and mass of product used were based on the 1987 Westat survey data, specifically the data found under the Adhesive Removers scenario and are listed in Table 2-75.

Table 2-75. Estimated[a] NMP Air Concentrations (Time Averaged Over 1 Day) Based on Residential Use of Adhesives Removers

Scenario Description For Product User (Women of Childbearing Age)	Duration of Use (min)	Weight Fraction (%)	Mass of Product Used (g)	Air Concentration [a]		
				Max 8 hr TWA (mg/m^3)	Max 8 hr TWA (ppm)	Max 24 hr TWA (ppm)
Adhesive Remover						
Medium Intensity Use [c]	60	18.90	213.17	1.42	0.349	0.119
High Intensity Use [b]	480	25.00	1,705.33	21.70	5.34	1.89

[a] See Appendix F for details about the model inputs and the method used to estimate air concentrations of NMP.
[b] Medium intensity use estimate based on using 50th percentile values for use patterns from Westat Survey (1987).
[c] High intensity use estimate based on using 90th percentile values for use patterns from Westat Survey, (1987).

The 'Adhesives/Caulk Removers' default scenario within the Consumer Exposure Module (CEM) was chosen for conducting the modeling runs. This selection was the closest match to the liquid adhesive remover scenario among the default CEM exposure scenarios. The common modeling inputs required to run CEM for all consumer scenarios evaluated in this assessment are provided in Table 2-71. Other scenario-specific input parameters are provided in Table 2-72.

CEM calculated air concentrations over the course of the simulation for the room of use and the rest of the house (Zone 1 and Zone 2). These concentrations were inputs to the PBPK model and used the body weight and respiration rate for adult women (+21) and young women (16-20) both considered of child-bearing age in calculating the internal dose of NMP.

Table 2-75 presents the results of the indoor air concentrations (ppm) both central tendency and high-end estimated exposures for the consumer use scenarios based on the 50th percentile and 95th percentile input parameters. Calculations detailing the conversion from acute dose rates to air concentrations are provided in a supplemental Excel spreadsheet file. (U.S. EPA, 2019d)

Detailed CEM modeling results are provided in Table 2-72.

Total internal NMP dose (Cmax) resulting from inhalation, dermal and vapor through skin exposures to women of childbearing age consumer use of adhesive remover products as estimated from the PBPK model is presented in Table 2-76.

Table 2-76. Estimated NMP Exposures (Time Averaged Over 1 Day) Based on Residential Use of Adhesive Removers

Scenario Description For Product User	Women of Childbearing Age Cmax (mg/L)	Pregnant Women Cmax (mg/L)
Adhesive Removers		
Medium Intensity Use	1.292	1.239
High Intensity Use	5.957	5.778

Auto Interior Liquid and Spray Cleaners

Exposure to NMP found in NMP-containing auto interior cleaner products was based on one product that was a liquid and one product that was a spray applied. The NMP weight fraction of the liquid cleaner was listed in the product Safety Data Sheet as a range between 1 and 5%. For the modeling scenarios, EPA assumed a typical or central tendency NMP amount of 3% and at a high-end of 5% NMP. The duration of use and mass of product used were based on the 1987 Westat survey data, specifically the data found under the Solvent-type Cleaning Fluids or Degreasers scenario and are listed in Table 2-77.

For the spray applied cleaner, the product data sheet listed the weight fraction as <1%. EPA conservatively used 1% for both scenarios with the other two parameters distinguishing the scenarios as either high-end or central tendency. The duration of use and mass of product used were based on the 1987 Westat survey data, specifically the data found under the Solvent-type Cleaning Fluids or Degreasers scenario and are listed in Table 2-77.

Table 2-77. Estimated[a] NMP Air Concentrations (Time Averaged Over 1 Day) Based on Residential Use of Auto Interior Liquid or Spray Cleaners

Scenario Description For Product User (Women of Childbearing Age)	Duration of Use (min)	Weight Fraction (%)	Mass of Product Used (g)	Air Concentration [a]		
				Max 8 hr TWA (mg/m^3)	Max 8 hr TWA (ppm)	Max 24 hr TWA (ppm)
Auto Interior Liquid Cleaner						
Medium Intensity Use [b]	15	3	7.69	2.88	0.711	0.237
High Intensity Use [c]	120	5	132.87	54.4	13.4	4.48
Auto Interior Spray Cleaner						
Medium Intensity Use [b]	15	1	7.69	10.8	0.266	8.89E-02
High Intensity Use [c]	120	1	132.87	12.0	2.95	0.984

[a] See Appendix F for details about the model inputs and the method used to estimate air concentrations of NMP.
[b] Medium intensity use estimate based on using 50th percentile values for use patterns from Westat Survey (1987).
[c] High intensity use estimate based on using 95th percentile values for use patterns from Westat Survey, (1987).

The 'All Purpose Liquid Cleaner' and the 'All Purpose Spray Cleaner' default scenarios within the Consumer Exposure Module (CEM) were chosen for conducting the modeling runs for the Auto Liquid Cleaner and Auto Spray Cleaner scenarios. This selection was the closest match to the liquid or spray cleaner scenario among the default CEM exposure scenarios. The common modeling inputs required to run CEM for all consumer scenarios evaluated in this assessment are provided in Table 2-71. Other scenario-specific input parameters are provided in Table 2-72.

CEM calculated air concentrations over the course of the simulation for the room of use and the rest of the house (Zone 1 and Zone 2). These concentrations were inputs to the PBPK model and used the body weight and respiration rate for adult women (+21) and young women (16-20) both considered of child-bearing age in calculating the internal dose of NMP (cite EPA definition of childbearing age).

Table 2-77 presents the results of the indoor air concentrations (ppm) both central tendency and high-end estimated exposures for the consumer use scenarios based on the 50th percentile and 95th percentile input parameters. Calculations detailing the conversion from acute dose rates to air concentrations are provided in a supplemental Excel spreadsheet file. (U.S. EPA, 2019d)

Total internal NMP dose (Cmax) resulting from inhalation, dermal and vapor through skin exposures to women of childbearing age consumer use of various auto interior cleaner products as estimated from the PBPK model is presented in Table 2-78.

Table 2-78. Estimated NMP Exposures (Time Averaged Over 1 Day) Based on Residential Use of Auto Interior Liquid or Spray Cleaners

Scenario Description For Product User	Women of Childbearing Age Cmax (mg/L)	Pregnant Women Cmax (mg/L)
Auto Interior Liquid Cleaner		
Medium Intensity Use	0.256	0.249
High Intensity Use	4.355	4.245
Auto Interior Spray Cleaner		
Medium Intensity Use	0.093	0.091
High Intensity Use	0.183	0.177

Cleaners/Degreasers, Engine Cleaner/Degreaser and Spray Lubricant

Exposure to NMP found in consumer cleaner/degreaser and spray lubricant products containing NMP was based on product data found on a total of 10 products. Eight products ranging from oven cleaners to metal cleaners to resin cleaner had NMP weight fractions, as listed in the product Safety Data Sheets, between 1% and 100%. The duration of use and mass of product used were based on the 1987 Westat survey data, specifically the data found under the Solvent-type Cleaning Fluids or Degreasers scenario and are listed in Table 2-79.

One product was specifically used as an engine cleaner (weight fraction between 15% and 40%) and one product was found as a spray lubricant (weight fraction between 30% to 40%). For the three modeling scenarios, EPA assumed the product could be available in a low-end formulation with 1% NMP, a typical or central tendency amount of 3% and at a high-end of 5% NMP. The duration of use and mass of product used were based on the 1987 Westat survey data, specifically the data found under the Engine Cleaners/Degreasers scenario and are listed in Table 2-79.

One product was identified as a mold release (i.e., once a product is formed or shaped then hardened in a mold, it then can be easily removed). It was modeled differently since it is used as a spray product. The duration of use and mass of product used were based on the 1987 Westat survey data, specifically the data found under the Other Lubricants scenario and are listed in Table 2-79.

Table 2-79. Estimated[a] NMP Air Concentrations (Time Averaged Over 1 Day) Based on Residential Use of Cleaners/Degreasers, Engine Cleaner/Degreaser and Spray Lubricant

Scenario Description For Product User (Women of Childbearing Age)	Duration of Use (min)	Weight Fraction (%)	Mass of Product Used (g)	Air Concentration [a]		
				Max 8 hr TWA (mg/m^3)	Max 8 hr TWA (ppm)	Max 24 hr TWA (ppm)
Cleaners/Degreasers						
Medium Intensity Use [b]	15	25.46	94.19	18.5	4.56	1.61
High Intensity Use [c]	120	29.87	927.43	235	57.9	20.8
Engine Cleaner/Degreaser						
Medium Intensity Use [b]	15	27.50	291.6	39.7	9.80	3.56
High Intensity Use [c]	120	40	1,206.60	281	69.3	25.5
Spray Lubricant						
Medium Intensity Use [b]	2	35	18.71	0.28	7.04E-02	2.48E-02
High Intensity Use [c]	30	40	170.05	2.65	0.65	0.23

[a] See Appendix F for details about the model inputs and the method used to estimate air concentrations of NMP.
[b] Medium intensity use estimate based on using 50th percentile values for use patterns from Westat Survey (1987).
[c] High intensity use estimate based on using 95th percentile values for use patterns from Westat Survey, (1987).

The 'All Purpose Liquid Cleaner', 'All Purpose Spray Cleaner' and 'Lubricant (spray)' default scenarios within the Consumer Exposure Module (CEM) were chosen for conducting the modeling runs for the Cleaner/Degreaser, Engine Cleaner/Degreaser and Spray Lubricant scenarios, respectively. This selection was the closest match to the liquid or spray cleaner scenario among the default CEM exposure scenarios. The common modeling inputs required to run CEM for all consumer scenarios evaluated in this assessment are provided in Table 2-71. Other scenario-specific input parameters are provided in Table 2-72.

CEM calculated air concentrations over the course of the simulation for the room of use and the rest of the house (Zone 1 and Zone 2). These concentrations were inputs to the PBPK model and used the body weight and respiration rate for adult women (+21) and young women (16-20) both considered of child-bearing age in calculating the internal dose of NMP.

Table 2-79 presents the results of the indoor air concentrations (ppm) both central tendency and high-end estimated exposures for the consumer use scenarios based on the 50th percentile and 95th percentile input parameters. Calculations detailing the conversion from acute dose rates to air concentrations are provided in a supplemental Excel spreadsheet file. (U.S. EPA, 2019d)

The total internal NMP dose (Cmax) resulting from inhalation, dermal and vapor through skin exposures to women of childbearing age consumer use of various types of cleaner/degreaser products as estimated from the PBPK model is presented in Table 2-80.

Table 2-80. Estimated NMP Exposures (Time Averaged Over 1 Day) Based on Residential Use of Cleaners/Degreasers, Engine Cleaner/Degreaser and Spray Lubricant

Scenario Description For Product User	Women of Childbearing Age Cmax (mg/L)	Pregnant Women Cmax (mg/L)
Cleaners/Degreasers		
Medium Intensity Use	1.033	1.016
High Intensity Use	13.40	13.00
Engine Cleaner/Degreaser		
Medium Intensity Use	1.682	1.640
High Intensity Use	16.46	15.97
Spray Lubricant		
Medium Intensity Use	0.332	0.322
High Intensity Use	2.853	2.801

Paint and Arts and Craft Paint

Exposure to NMP found in consumer paint and arts and crafts paint products containing NMP was based on product data found on a total of four products. Two paint products that contained NMP were paints such as concrete paint and truck bed coating and had NMP weight fractions ranging from 1% to 7%. For arts and crafts paint the NMP weight fractions were 0.1% to 1%. The duration of use and mass of product used were based on the 1987 Westat survey data, specifically the data found under the Latex Paint scenario and are listed in Table 2-79. For the Arts and Craft scenario mass of product was adjusted lower (ratio of 64) by the craft volume sold (2 ounces) relative to the wall paint (gallon).

Table 2-81. Estimated[a] NMP Air Concentrations (Time Averaged Over 1 Day) Based on Residential Use of Paint and Arts and Crafts Paint

Scenario Description For Product User (Women of Childbearing Age)	Duration of Use (min)	Weight Fraction (%)	Mass of Product Used (g)	Air Concentration [a]		
				Max 8 hr TWA (mg/m^3)	Max 8 hr TWA (ppm)	Max 24 hr TWA (ppm)
Paint						
Medium Intensity Use [b]	180	2.03	4,194.24	2.40	0.593	0.204
High Intensity Use [c]	810	3.63	23,068.31	18.3	4.51	2.52
Arts and Crafts						
Medium Intensity Use [b]	180	0.55	65.30	1.41E-02	3.48E-03	1.19E-03
High Intensity Use [c]	810	1.00	359.00	1.01E-01	2.48E-02	1.39E-02

[a] See Appendix F for details about the model inputs and the method used to convert acute dose rates (ADRs) to air concentrations of NMP.

Scenario Description For Product User (Women of Childbearing Age)	Duration of Use (min)	Weight Fraction (%)	Mass of Product Used (g)	Air Concentration [a]		
				Max 8 hr TWA (mg/m^3)	Max 8 hr TWA (ppm)	Max 24 hr TWA (ppm)
[b] Medium intensity use estimate based on using 50th percentile values for use patterns from Westat Survey (1987).						
[c] High intensity use estimate based on using 95th percentile values for use patterns from Westat Survey, (1987).						

The 'Solvent-based Wall Paint' and the 'Crafting Paint' default scenarios within the Consumer Exposure Module (CEM) were chosen for conducting the modeling runs for the Paint and Arts and Crafts scenarios, respectively. These selections were the closest match to each of the paint scenarios among the default CEM exposure scenarios. The common modeling inputs required to run CEM for all consumer scenarios evaluated in this assessment are provided in Table 2-71. Other scenario-specific input parameters are provided in Table 2-72.

CEM calculated air concentrations over the course of the simulation for the room of use and the rest of the house (Zone 1 and Zone 2). These concentrations were inputs to the PBPK model and used the body weight and respiration rate for adult women (+21) and young women (16-20) both considered of child-bearing age in calculating the internal dose of NMP.

Table 2-81 presents the results of the indoor air concentrations (ppm) both central tendency and high-end estimated exposures for the consumer use scenarios based on the 50th percentile and 95th percentile input parameters. Calculations detailing the conversion from acute dose rates to air concentrations are provided in a supplemental Excel spreadsheet file (U.S. EPA, 2019d).

Detailed CEM modeling results are provided in Table 2-72.

Total internal NMP dose (Cmax) resulting from inhalation, dermal and vapor through skin exposures to women of childbearing age consumer use of paint products as estimated from the PBPK model is presented in Table 2-82.

Table 2-82. Estimated NMP Exposures (Time Averaged Over 1 Day) Based on Residential Use of Paints and Arts and Crafts Paints

Scenario Description For Product User	Women of Childbearing Age Cmax (mg/L)	Pregnant Women Cmax (mg/L)
Paints		
Medium Intensity Use	0.374	0.358
High Intensity Use	1.422	1.415
Arts and Crafts Paints		
Medium Intensity Use	0.071	0.068
High Intensity Use	0.222	0.219

Stains, Varnishes, Finishes (Coatings)

Exposure to NMP found in consumer stains, varnishes, finishes and other coatings products containing NMP was based on product data found on a total of nine products. The NMP weight fractions range was between 0.3% to 10% with the mean of 4.97% and the average high-end of 8.25% used to model consumer exposure estimates. The duration of use and mass of product used were based on the 1987 Westat survey data, specifically the data found under the Stains, Varnishes, and Finishes scenario and are listed in Table 2-83.

The 'Varnishes and Floor Finishes' default scenarios within the Consumer Exposure Module (CEM) was chosen for conducting the modeling runs for the Stains, Varnishes, Finishes (Coatings) scenario. This selection was the closest match to the liquid coatings scenario among the default CEM exposure scenarios. The common modeling inputs required to run CEM for all consumer scenarios evaluated in this assessment are provided in Table 2-71. Other scenario-specific input parameters are provided in Table 2-72.

Table 2-83. Estimated[a] NMP Air Concentrations (Time Averaged Over 1 Day) Based on Residential Use of Stains, Varnishes, Finishes (Coatings)

Scenario Description For Product User (Women of Childbearing Age)	Duration of Use (min)	Weight Fraction (%)	Mass of Product Used (g)	Air Concentration [a]		
				Max 8 hr TWA (mg/m^3)	Max 8 hr TWA (ppm)	Max 24 hr TWA (ppm)
Stains, Varnishes, Finishes (Coatings)						
Medium Intensity Use [b]	60	4.97	366.42	6.84E-01	1.68E-01	5.74E-02
High Intensity Use [c]	360	8.25	3,908.44	12.5	3.08	1.08

[a] See Appendix F for details about the model inputs and the method used to estimate air concentrations of NMP.
[b] Medium intensity use estimate based on using 50th percentile values for use patterns from Westat Survey (1987).
[c] High intensity use estimate based on using 95th percentile values for use patterns from Westat Survey, (1987).

CEM calculated air concentrations over the course of the simulation for the room of use and the rest of the house (Zone 1 and Zone 2). These concentrations were inputs to the PBPK model and used the body weight and respiration rate for adult women (+21) and young women (16-20) both considered of child-bearing age in calculating the internal dose of NMP.

Table 2-83 presents the results of the indoor air concentrations (ppm) both central tendency and high-end estimated exposures for the consumer use scenarios based on the 50th percentile and 95th percentile input parameters. Calculations detailing the conversion from acute dose rates to air concentrations are provided in a supplemental Excel spreadsheet file. (U.S. EPA, 2019d)

Total internal NMP dose (Cmax) resulting from inhalation, dermal and vapor through skin exposures to women of childbearing age consumer use of coatings products as estimated from the PBPK model is presented in Table 2-84.

Table 2-84. Estimated NMP Exposures (Time Averaged Over 1 Day) Based on Residential Use of Stains, Varnishes, Finishes (Coatings)

Scenario Description For Product User	Women of Childbearing Age Cmax (mg/L)	Pregnant Women Cmax (mg/L)
Stains, Varnishes, Finishes (Coatings)		
Medium Intensity Use	0.341	0.327
High Intensity Use	1.947	1.882

Paint Removers

Consumer exposure to NMP found in consumer paint remover products containing NMP was assessed in the Final *Paint Remover Risk Assessments* (U.S. EPA, 2015) as well as the *Supplemental Consumer Exposure and Risk Estimation Technical Report for NMP in Paint and Coating Removal* (see 6F.2). For the supplemental analysis, exposures were estimated for 18 scenarios. The E2 scenario was selected as a representative high intensity use scenario. The paint remover product was modeled to remove paint from a bathtub and using 4 applications. The A2 scenario was selected as a representative medium intensity use scenario. The NMP paint remover product was used to remove paint from a coffee table. The weight fraction for paint remover products was 50% for both scenarios. Appendix F.2 lists all of the evaluated scenarios for the paint remover evaluation.

Table 2-85. Estimated NMP Air Concentrations (Time Averaged Over 1 Day) Based on Residential Use Paint Removers

Scenario Description For Product User	Duration of Use (min)	Weight Fraction (%)	Mass of Product Used (g)	Air Concentration	
				Max 8 hr TWA (mg/m^3)	Max 8 hr TWA (ppm)
Paint Removers					
Medium Intensity Use	60	50	540	3.24	0.8
High Intensity Use	360	50	1944	146	36.0

As described in detail in the previous assessments, emissions data were available specifically for paint remover product use. This data can then be used in a higher tier exposure model, the MCCEM to estimate air concentration. In principle, as in the CEM, the MCCEM also estimates NMP air concentrations in various areas of the house depending on the user's activity pattern. MCCEM calculated air concentrations over the course of the simulation for the room of use and the rest of the house (Zone 1 and Zone 2). These concentrations were inputs to the PBPK model and used the body weight and respiration rate for adult women of child-bearing age in calculating the internal dose of NMP.

Table 2-86 presents the internal dose for women of childbearing age for the medium intensity use and high intensity use scenarios.

Table 2-86. Estimated NMP Exposures (Time Averaged Over 1 Day) Based on Residential Use of Paint Removers

Scenario Description For Product User	Women of Childbearing Age Cmax (mg/L)
Paint Removers	
Medium Intensity Use	2.02
High Intensity Use	10.02

EPA reviewed data from one study that specifically measured NMP air concentrations while an NMP-containing paint removal product was being used on floors in a house undergoing renovation (Kiefer, 1994). The study reported air concentrations ranging from 3.6 to 7.7 ppm in the room of use. In EPA's supplemental analysis of NMP use in paint and coating removal, the modeled paint removal use resulted in air concentrations of 11.1 ppm (8-hr time weighted average). Although this estimated NMP air concentration is higher than the measured air concentration presented by Kiefer et al. (1994), both represent the air concentration in the room that a non-user would be exposed to rather than the personal breathing zone concentration to which the user is directly exposed. EPA determined that the estimated NMP exposures incurred during floor paint removal do not present a risk to non-users (See Appendix F.2).

Exposure to Bystanders

In each of the consumer scenarios listed above, use of a product containing NMP is expected to result in air concentrations of NMP and user inhalation exposure to NMP in addition to dermal and vapor-through skin exposures. EPA also expects that the NMP air concentrations can be circulated through the house via the air ventilation system so that NMP exposures could occur to other occupants in the house during and after consumer use. The air concentration in Zone 2 (rest of the house) is presented in the supplemental document, *Risk Evaluation for N-Methylpyrrolidone, Supplemental Information on Consumer Exposure Assessment, Consumer Exposure Model Outputs* (U.S. EPA, 2019d).

EPA estimated the internal dose for indirect NMP exposures adult bystanders as well as children aged 3-5 years due to their location in the house during consumer use (see Table 2-85) (U.S. EPA, 2019e).

Table 2-87. Estimated Bystander Exposure to NMP Consumer Use

Consumer Conditions of Use	Bystander Female Adult Cmax (mg/L)	Bystander Child (3-5 yrs) Cmax (mg/L)
Cleaners/ Degreasers	4.06	4.76
Engine Cleaner/ Degreaser	5.55	6.51

2.4.2.6 Key Assumptions and Confidence

Given the absence of direct measurement and monitoring of consumer exposures during product use, modeling was used to evaluate consumer exposures resulting from the conditions of use summarized in Table 2-72. Modeling requires a number of input parameters, some of which rely on default modeling assumptions and some of which rely on user inputs or selections. As with any modeling approach, there are uncertainties associated with the assumptions and data used. An overall review of these factors can help develop a qualitative description of the confidence associated with the modeling approach and results.

Key Assumptions:

Evaluation of acute consumer exposure is based on the assumption that the products used under the conditions of use summarized in Table 2-72, except paint removers, are only used once per day. This assumption considers a single use event which may occur over a 24-hour period and represents an expected consumer use pattern. This is a reasonable assumption for the average intensity user but may underestimate those high intensity users such as do-it-yourselfers (DIY) that could use a product multiple times in a day. The paint remover scenario as defined in the Paint Remover Risk Assessment, defines a user pattern in which the product is applied then scraped away with the paint and reapplied again as is outlined in the product directions. This product-specific use is reflected in the use patterns for all of the products evaluated for consumer exposures.

Evaluation of consumer exposure for this evaluation is also based on the assumption that a consumer uses a single product or product type. For the products estimated under the conditions of use, this is a reasonable assumption. However, this assumption may, in general, underestimate NMP exposures since NMP is also found in cosmetic products and other personal care products that could be used concurrently.

This evaluation assumes consumer exposure is not chronic in nature. This assumption is based on the expected consumer use pattern and data found during systematic review that indicates frequency of use (days of use) of products containing the chemical of concern is not chronic in nature. This assumption is also based on the fairly rapid elimination of NMP so that the use pattern and data would not be chronic in nature. This assumption may result in excluding certain consumer users who may be do-it-yourselfers.

This evaluation assumes a background concentration of zero for the chemical of concern during evaluation of consumer exposure. This assumption is primarily driven by the physical chemical properties of the chemical of concern which is the high vapor pressure and expected quick dissipation of the chemical of concern.

Inputs

Inputs for the modeling were a combination of physical chemical properties of the chemical of concern, default values within the models used, values from the Exposure Factors Handbook (U.S. EPA, 2011), and use pattern survey data found in the literature as part of the systematic review process (Westat Survey (U.S. EPA, 1987)). Physical chemical properties of the chemical of concern are pre-defined and well established in the literature. These properties do not change under standard conditions and therefore have high confidence associated with them.

Default values within the models used are a combination of central tendency and high-end values derived from well-established calculations, modeling, literature, and from the Exposure Factors Handbook (U.S. EPA, 2011). The models used have a wide variety of parameters with default values, although certain default values can be changed (if information and data are available) prior to running the model. There is a high confidence associated with these values due to the number of parameters where defaults are available.

Values from the Exposure Factors Handbook (U.S. EPA, 2011) are a combination of central tendency and high-end values which are well established and commonly used for exposure evaluations and modeling. The values are derived from literature, modeling, calculations, and surveys. There is a high confidence associated with the Exposure Factors Handbook (U.S. EPA, 2011).

The Westat Survey (U.S. EPA, 1987) was previously described in this evaluation. It is an EPA-directed national survey which received over 4,920 completed questionnaires from across the United States. The survey aimed to answer multiple questions related to the use of solvent-containing consumer products within thirty-two different common household product categories. Multiple aspects of the survey and survey results were utilized in this evaluation. Most of the consumer uses summarized in Table 2-72 aligned well with one of the thirty-two product categories within the Westat Survey. There is a high confidence associated with cross-walking of consumer uses with the Westat product categories.

The representativeness of the consumer use patterns (duration of use, amount used, room of use, etc.) described in the Westat Survey (from 1987) is believed to remain strong when compared to present day consumer use patterns even though some aspects of the use may have changed (electronics cleaners were applied to VCRs in 1987, but now are applied to computer motherboards or DVD players). However, ease of access to products on-line or in big box stores (like home improvement stores), readily accessible how-to videos, and a consumer movement toward more do-it-yourself projects with products containing the chemical of concern could impact the representativeness of the consumer use patterns

described within the Westat Survey and may lead to an underestimate of overall consumer exposure. There is a high confidence associated with the representativeness of the consumer use patterns described within the Westat Survey and present-day consumer use patterns.

Other Uncertainties:
There are several other factors to which some level of uncertainty may apply. These include, but are not limited to, product use/availability, model specific factors, building characteristics, and use of personal protective equipment or natural/engineered controls.

As described in Section 2.4.2.1, the market profile was developed in 2017 based on information available at that time. These do not take into consideration company-initiated formulation changes, product discontinuation, or other business or market-based factors that occurred after the documents were compiled. However, unless these factors were in process while the dossier and market profile were being developed, it is unlikely any significant changes occurred since such changes often require considerable time to research, develop, and implement. Even with discontinuation of products, while they may readily be removed from shelves, product already purchased or picked up to be sold online shortly before discontinuation will take some time to work out of the system. There is a medium confidence associated with the product use/availability of product containing the chemical of concern.

There are multiple model specific factors to which a level of uncertainty may apply including user groups (age groups), building characteristics, and inherent model parameters.

There are multiple building characteristics considered when modeling consumer exposure including, but not limited to, room size, ventilation rate, and building size. For this evaluation, we relied on default values within the models for these parameters. These default values were primarily obtained from the Exposure Factors Handbook (U.S. EPA, 2011). There is a medium to high confidence associated with these parameters.

Room size varied for this evaluation based on room of use obtained from the Westat Survey (1987) data. Room size relates to the volume of the room and is a sensitive parameter within the models. However, the room size of a standard bedroom, living room, kitchen, utility room, one or two car garage, etc. should be relatively consistent across building types (small or large residential homes, apartments, condominiums, or townhomes). Therefore, any uncertainty associated with room size is derived more from the room of use selected, rather than the wide variety of sizes of a particular room of use. Since the rooms of use selected for this evaluation are based on data collected by the Westat Survey, there is a high confidence associated with room sizes used for this evaluation.

Ventilation rate is another sensitive parameter within the models. Similar to the room of use, however, ventilation rates should be relatively consistent across building types where ventilation systems are properly maintained and balanced. Centralized ventilation systems are designed to deliver ventilation rates or air exchange rates which meet the American Society of Heating, Refrigeration, and Air Conditioning Engineers Standard Recommendations which are established for rooms, house types, commercial buildings, and others. Centralized ventilation systems may be larger for larger homes, but the ventilation rates delivered to the specific room of use should be relatively consistent across building types. Therefore, any uncertainty associated with ventilation rates is derived more from the proper design, balancing, and maintenance of ventilation systems. Ventilation rates for a particular room of use

could be impacted by use of fans or opening windows within the room of use, however, most respondents to the Westat Survey indicated they did not have an exhaust fan on when using the products. Most respondents kept the door to the room of use open but did not open doors or windows leading to the outside when using the products. There is a medium to high confidence associated with the ventilation rates used for this evaluation.

Building size is another sensitive parameter within the models, however, the sensitivity derives from more mixing and dissipation outside of the room of use. There will be more variability in building size across building types so there is a medium confidence associated with building size.

The use of personal protective equipment or natural/engineered controls by a consumer during product use is uncertain. It is not expected that consumers will utilize personal protective equipment like full face respirators, or engineering controls like hoods when using consumer products in a residence or building to reduce inhalation risks. While it may be slightly more likely that, for certain products, consumers may choose to wear gloves or eye protection, neither of these address inhalation exposure. Use of gloves by a consumer could decrease dermal exposure, assuming the gloves are high quality and chemical resistant. Latex gloves are readily available; however, such gloves tear easily, and may not be resistant to breakdown by certain products used. Although the use of gloves could reduce dermal exposure, if used improperly (for example fully immersing hands into a product) could allow for leakage into the glove.

Confidence:

There is an overall medium confidence in all the results found for the consumer scenarios identified in Table 2-68 and evaluated in this evaluation. This confidence derives from a review of the factors discussed above as well as previous discussions about the strength of the models and data used, sensitivity of the models, and approaches taken for this evaluation.

The models used for this evaluation are peer reviewed models. The equations are derived, justified and substantiated by peer reviewed literature as described in the respective user guides and associated user guide appendices. The default values utilized in the model (and retained for this evaluation) are a combination of central tendency and high-end estimates from both peer reviewed literature and the Exposure Factors Handbook (U.S. EPA, 2011) providing a representative spectrum of modeling results. Even though some values have high end values (like building size or ventilation rates), it should be recognized that these parameters are correlated, and that "higher" building sizes or higher ventilation rates would be expected to result in more mixing and dissipation leading to a lower exposure.

The data used in lieu of default values within the model are a combination of central tendency, and high-end values from the Westat Survey, which was rated as a high-quality study as part of the systematic review process. The twelve use scenarios evaluated for this evaluation aligned well with specific scenarios within the Westat Survey, pre-defined model scenarios, and other approaches taken. The deterministic approach taken for consumer exposure in this evaluation involved varying three parameters that were either highly sensitive or representative of consumer use patterns or both. The three parameters varied also provided a broad spectrum of consumer use patterns covering low, moderate, and high intensity uses and therefore are not limited to a high-end, worst-case type situation or an upper bounding estimate. Other aspects of the deterministic approach taken (like a single product used once per day) may result in an underestimate of actual consumer exposure.

2.5 Other Exposure Considerations

2.5.1 Potentially Exposed or Susceptible Subpopulations

TSCA § 6 requires that a risk evaluation "determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of cost or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation by the Administrator, under the conditions of use." TSCA § 3(12) states that "the term 'potentially exposed or susceptible subpopulation' means a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly."

In developing the draft risk evaluation, EPA analyzed reasonably available information to ascertain whether some human receptor groups may have greater exposure potential or susceptibility to NMP than the general population. Because risk determinations were based on potential reproductive and developmental effects of NMP exposure that may occur at sensitive lifestages, they account for risks to susceptible subpopulations, including pregnant women, children, adolescents, and men and women of reproductive age. It was assumed that exposures which do not result in unreasonable risks for this population would also be protective of other populations because other health effects are expected to occur at high levels of NMP exposure.

EPA estimated exposures to children who may be located near the consumer user at the time of use and determined that these exposures were below the levels of concern identified for adverse developmental effects and would therefore be below the levels of concern for other hazard effects that may be associated with higher NMP exposure levels.

2.5.2 Aggregate and Sentinel Exposures

As a part of risk evaluation, Section 2605(b)(4)(F)(ii) of TSCA requires EPA to describe whether aggregate or sentinel exposures were considered under the identified conditions of use and the basis for their consideration. EPA has defined aggregate exposure as "the combined exposure to an individual from a single chemical substance across multiple routes and multiple pathways." (40 C.F.R. 702.33). EPA defines sentinel exposure as "exposure to a single chemical substance that represents the plausible upper bound relative to all other exposures within a broad category of similar or related exposures." (40 C.F.R. 702.33). EPA considered sentinel exposure in the form of high-end estimates for consumer and occupational exposure scenarios which incorporate dermal and inhalation exposure, as these routes are expected to present the highest exposure potential based on details provided for the manufacturing, processing and use scenarios discussed in the previous section. The exposure calculation used to estimate dermal exposure to liquid is conservative for high-end occupational and consumer scenarios where it assumes full contact of both hands and no glove use.

3 HAZARDS

3.1 Environmental Hazards

3.1.1 Approach and Methodology

EPA identified environmental hazard data for NMP through an extensive literature search as described in detail in Section 1.5 and depicted in Figure 1-8. This process was completed in 2019 as part of this RE with a portion of the search completed in 2017 as part of the NMP problem formulation.

EPA in the NMP Problem Formulation (U.S. EPA, 2018c) did not conduct any further analyses on pathways of exposure for terrestrial receptors in line with Section 2.5.3.1. The Problem Formulation did not identify Environmental Hazards for either aquatic or terrestrial receptors. The analysis was based on a qualitative assessment of the physical-chemical properties and fate of NMP in the environment and a quantitative comparison of the hazards and exposures identified for aquatic organisms.

Subsequent to that analysis, an additional five "Key/Supporting" citations were identified by EPA after review of the OECD HPV SIDS Document for NMP (OECD, 2009b). EPA obtained the full study reports from the NMP Producer's Group (BASF and GAF). As these studies raised concerns for Environmental Hazards associated with NMP and aquatic receptors, a quantitative evaluation of hazards to aquatic receptors is included as part of this RE. EPA conducted no further analyses of exposure and hazards for terrestrial receptors and instead relied on the analyses conducted as part of the NMP Problem Formulation.

3.1.2 Hazard Identification

EPA quantitatively evaluated impacts to aquatic organisms, including fish, aquatic invertebrates and algae from acute and chronic NMP releases to surface water. The hazard characterization for all identified environmental hazard endpoints are summarized in Table 3-1. The environmental hazard data were reviewed for acute and chronic exposure duration related endpoints (e.g., mortality, growth, immobility, reproduction). No ecotoxicity studies were identified for sediment-dwelling organisms.

3.1.2.1 Toxicity Data for Aquatic Organisms

EPA evaluated four studies for NMP acute exposures for fish. The acute 96-hour LC_{50} values reported for fish range from >500 mg/L for the freshwater rainbow trout (*Oncorhynchus mykiss*) to 4,030 mg/L for the freshwater orfe (*Leuciscus idus*).

For NMP acute toxicity data were evaluated for aquatic invertebrates for four species including the freshwater water flea (*Daphnia magna*), the saltwater grass shrimp (*Palaemonetes vulgaris*), the saltwater mud crab (*Neopanope texana sayi*), and the freshwater scud (*Gammarus sp.*) (GAF, 1979). The results of these studies are summarized in Table 3-1 with more detail provided in Appendix G. The 48-hr EC_{50} for NMP and *D. magna* is reported as 4,897 mg/L. The 96-hr LC_{50} 's for grass shrimp, mud crab, and scud are reported as 1,107, 1,585 and 4,655 mg/L, respectively (GAF, 1979).

For the fresh water green algae (*Scenedesmus subspicatus*), the 72-hr EC_{50} values were 600 mg/L (Biomass) and 673 mg/L (Growth rate) (BASF AG, 1989).

EPA evaluated one chronic toxicity study for NMP exposures for freshwater invertebrates (*D. magna*). A 21-day study with *D. magna* reported reproductive effects for NMP with a No-Observed Effect Concentration (NOEC) of 12.5 mg/L and a Lowest Observed Effect Concentration of 25 mg/L, resulting in a calculated chronic toxicity value of 17.68 mg/L (geometric mean of NOEC and LOEC) (BASF AG, 2001).

Chronic aquatic toxicity data are not available for NMP for fish. EPA estimated a chronic fish toxicity value based on an acute to chronic ratio (ACR) approach extrapolating from the acute fish toxicity data. The acute 96-hour LC_{50} value for rainbow trout of >500 mg/L was divided by 10 resulting in an estimated chronic fish toxicity value for NMP of >50 mg/L.

EPA evaluated one chronic aquatic toxicity study for aquatic plants. The green algae (*Scenedesmus subspicatus*) was exposed to NMP for 72-hours. The NOEC value for NMP was reported at 125 mg/L and the LOEC at 250 mg/L. EPA calculated a chronic toxicity value of 177 mg/L (geometric mean of NOEC and LOEC) (BASF AG, 1989).

Table 3-1. Aquatic Toxicity Data for NMP

Duration	Test Taxa	Endpoint	Hazard value*	Units	Effect Endpoint	Reference
Acute	Fish	96-hour LC_{50}	>**500-4,030**	mg/L	Mortality	(BASF AG, 1983) (High); (BASF AG, 1986)
	Aquatic invertebrates	48/96 hour EC_{50}/LC_{50}	**1,107 – 4,897**	mg/L	Immobilization/Mortality	(GAF, 1979)
	Algae	72-hour EC_{50}	**600** (Biomass) **673** (Growth rate)	mg/L	Growth	(BASF AG, 1989)
	Acute Concentration of Concern (COC)		>100	mg/L	Estimated by dividing lowest reported acute value across test organisms (<500) by an Application Factor (AF) of 5	
Chronic	Fish	Chronic Value (ChV)	>50	mg/L	Estimated by dividing lowest reported acute value for fish (>500) by an acute to chronic ratio of 10.	
	Aquatic invertebrates	NOEC LOEC	**12.5 (Reported) 25 (Reported)**	mg/L	Reproduction	(BASF AG, 2001)[a]
		Chronic Value	17.7	mg/L	Estimated by calculating the geometric mean of the NOEC and LOEC.	
	Algae	NOEC LOEC	**125 (Reported) 250 (Reported)**	mg/L	Growth	(BASF AG, 1989)
		Chronic Value	177	mg/L	Estimated by calculating the geometric mean of the NOEC and LOEC	
	Chronic Concentration of Concern (COC)		1.77	mg/L	Lowest calculated or reported chronic value across taxa divided by an AF of 10.	

*Values in the tables are presented as reported by the study authors; **Bold** = experimental data

[a] Reservation of Rights: BASF has agreed to share this toxicity study report ("Study Report") with US EPA, at its written request, for EPA 's use in implementing a statutory requirement of the Toxic Substances Control Act ("TSCA "). Every other use, exploitation, reproduction, distribution, publication or submission to any other party requires BASF's written permission, except as otherwise provided by law. The submission of this Study Report to a public docket maintained by the United States Environmental Protection Agency is not a waiver of BASF's ownership rights. No consent is granted for any other third-party use of this Study Report for any purpose, in any jurisdiction. Specifically, and by example, no consent is granted allowing the use of this Study Report by a private entity in requesting any regulatory status, registration or other approval or benefit, whether international, national, state or local, including but not limited to the Regulation Evaluation Authorization and Restriction of Chemicals ("REACH") regulation administered by European Chemicals Agency ("ECHA"), an agency of the European Union.

3.1.2.2 Concentrations of Concern Calculation

Acute and chronic COCs were calculated for environmental toxicity of NMP using assessment factors. EPA applied an assessment factor (AF) according to EPA methods (U.S. EPA, 2013b, 2012d). The application of AFs provides a lower bound effect level that would likely encompass more sensitive species not specifically represented by the available experimental data. AFs can also account for differences in inter- and intra-species variability, as well as laboratory-to-field variability. These AFs are dependent on the availability of datasets that can be used to characterize relative sensitivities across multiple species within a given taxa or species group. However, they are often standardized in risk assessments conducted under TSCA, since the data available for most industrial chemicals are limited. For fish and aquatic invertebrates (e.g., daphnia) the acute toxicity values are divided by an AF of 5. For

chronic COCs, an AF of 10 is used. The COC for the aquatic plant endpoint is determined based on the lowest value in the dataset and application of an AF of 10 (U.S. EPA, 2013b, 2012d).

After applying AFs, EPA converts COC units from mg/L to µg/L (or ppb) in order to more easily compare COCs to surface water concentrations during risk characterization.

Acute COC

To derive an acute COC for NMP, EPA used the lowest reported acute toxicity value across taxa (>500 mg/L) and divided by the AF of 10 and multiplied by 1,000 to convert from mg/L to µg/L, or ppb.

The acute COC = (>500 mg/L) / AF of 5 = 100 mg/L x 1,000 = 100,000 µg/L or ppb.

- The acute COC for NMP is 100,000 ppb.

Chronic COC

The chronic COC for NMP was derived by EPA by dividing the aquatic invertebrate 21-day chronic toxicity value of 17.7 mg/L (1,768 µg/L) by an assessment factor of 10.

The acute COC = (17.7 mg/L) / AF of 10 = 1.77 mg/L x 1,000 = 1,770 µg/L or ppb.

- The chronic COC for NMP is 1,770 ppb.

3.1.2.3 Toxicity to Soil/Sediment and Terrestrial Organisms

EPA did not further evaluate in this RE exposure pathways (and hazards) associated with NMP in sediments and soils based on analyses completed as part of the NMP Problem Formulation (U.S. EPA, 2018c).

3.1.3 Weight of Scientific Evidence

During the data integration stage of EPA's systematic review for risk evaluation, EPA analyzed, synthesized, and integrated the data/information. This involved weighing scientific evidence for quality and relevance, using a Weight of Scientific Evidence (WOE) approach (U.S. EPA, 2016). In the June 2018 Problem Formulation for N-Methylpyrrolidone (NMP) (U.S. EPA, 2018c), seven studies were used to conduct a basic screening-level characterization the environmental hazards of NMP. At the time of the problem formulation, none of these studies identified during the literature search or ECHA summaries had been evaluated according to the systematic review criteria. Since the NMP Problem Formulation (U.S. EPA, 2018c) these studies have been evaluated according to the systematic review criteria in The Application of Systematic Review in TSCA Risk Evaluations (U.S. EPA, 2018a).

While EPA determined that there were enough environmental hazard data to characterize environmental hazards of NMP, there are uncertainties. First, assessment factors (AFs) were used to calculate the acute and chronic concentrations of concern for NMP. AFs account for differences in inter- and intra-species variability, as well as laboratory-to-field variability and are routinely used within TSCA for assessing

the hazard of new industrial chemicals (with very limited environmental test data). Some uncertainty may be associated with the use of the specific AFs used in the hazard assessment.

Second, more acute duration data were available in the literature than chronic duration data. Therefore, EPA is less certain of chronic hazard values than the acute hazard values. The most sensitive taxonomic group from the acute duration data, aquatic invertebrates, has chronic duration data available in the literature. Because the chronic fish data were not available, the chronic fish endpoint was addressed using the acute to chronic ratio (AF=10). The fish chronic toxicity value was estimated to be >50 mg/L.

3.1.4 Summary of Environmental Hazard

The acute 96-hour LC_{50} values for fish range from >500 mg/L to 4,030 mg/L. The acute EC_{50}/LC_{50} for aquatic invertebrates range from 1,107 mg/L to 4,897 mg/L. For fresh water green algae, the 72-hr EC_{50} values were 600 mg/L (Biomass) and 673 mg/L (Growth rate). EPA calculated the acute COC to be 100,000 µg/L (10 mg/L).

For the chronic fish endpoint, an acute to chronic ratio (ACR) approach was used to extrapolate a chronic toxicity value for NMP for fish based on the reported acute values. EPA calculated a chronic fish toxicity value for NMP of >50 mg/L using an ACR of 10 and the lowest reported acute toxicity value of >500 mg/L. For the aquatic invertebrate endpoint, a 21-day chronic toxicity value of 17.68 mg/L was calculated for NMP based on reproduction (geometric mean of the reported NOEC of 12.5 mg/L and LOEC of 25 mg/L). For the chronic aquatic plant endpoint, a 72-hour chronic toxicity value of 177 mg/L was calculated for NMP based on growth inhibition (geometric mean of the reported NOEC of 125 mg/L and the LOEC of 250 mg/L). EPA calculated the chronic COC 1,770 µg/L (1.77 mg/L).

The aquatic toxicity studies used to characterize the effects of acute and chronic NMP exposure to aquatic invertebrates are summarized in Table 3 1.

3.2 Human Health Hazards

3.2.1 Approach and Methodology

EPA identified hazard data for NMP through an extensive literature search as described in EPA's *Strategy for Conducting Literature Searches for NMP: Supplemental Document to the TSCA Scope Document* (U.S. EPA, 2017d). Only the identified "on-topic" references (as explained in the *N-Methylpyrrolidone (CASRN 872-50-4) Bibliography: Supplemental File for the TSCA Scope Document* (U.S. EPA, 2017b)) obtained from the human health hazard literature search were considered as relevant data/information sources for consideration in this draft risk evaluation of NMP. EPA's inclusion criteria were used to screen the initial literature search results (n = 1,397); 1,361 references were excluded based on PECO. In addition, three key/supporting studies were identified outside of this process and included in the current evaluation. The remaining hazard studies (n=36) were then evaluated using the data quality evaluation criteria for human health hazard studies as outlined in *The Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). The hazard data determined to be acceptable

based on this data quality review were extracted and integrated. This systematic review process is summarized in Figure 3-1.

The human health hazard of NMP has been examined in several publications (EC, 2016; Danish Ministry of the Environment, 2015; U.S. EPA, 2015; NICNAS, 2013; OECD, 2009b; U.S. EPA, 2006b; WHO, 2001). EPA relied heavily on the hazard information presented in these documents to inform the human health hazard identification and the dose-response analysis. EPA also evaluated studies that were published since these reviews during the analysis phase of the risk evaluation, as identified in the literature search conducted by the Agency for NMP (*NMP (CASRN 872-50-4) Bibliography: Supplemental File for the TSCA Scope Document* (U.S. EPA, 2017e).

Brief summaries for each hazard endpoint are presented in Section 3.2.3. Detailed information about study quality review for study selection is provided in Section 1.5.1. Developmental and reproductive toxicity endpoints were evaluated for consistency, sensitivity and relevance (Section 3.2.3). Based on the conclusions of previous assessments and a review of available studies, EPA narrowed the focus of the NMP hazard characterization to specific reproductive and developmental toxicity endpoints, reduced fertility, including fetal resorptions (mortality) and growth retardation. EPA conducted a dose-response assessment for these endpoints (Section 3.2.5), using benchmark dose analysis and PBPK model estimates of internal doses (Section 3.2.5.6) to select points of departure (POD) for use in the risk evaluation (Section 4.2).

EPA considered new (on-topic) studies with information on acute and non-cancer endpoints for hazard identification and dose-response analysis if the study received an overall data quality rating of high, medium, or low as described in the Application of Systematic Review in TSCA Risk Evaluations (U.S. EPA, 2018a). EPA has not developed data quality criteria for all types of relevant information (e.g., toxicokinetic data); however, this information was used to support the risk evaluation. Information that was rated unacceptable was not included in the risk evaluation. The human health hazard data used to characterize the effects of acute and chronic NMP exposure to humans are summarized in Table 3-12.Table 3-10. Additional information on the human health hazard endpoints considered during hazard identification, are provided in Appendix H. The comprehensive results of the study evaluations can be found in *NMP (872-50-4) Systematic Review: Supplemental File for the TSCA Risk Evaluation Document* (EPA-HQ-OPPT-2019-0236).

The human health hazard information was integrated using a strategy that includes consideration of the weight of the scientific evidence for each hazard endpoint to select the data used for dose-response assessment. The weight of scientific evidence analysis included integrating information from toxicokinetics and toxicodynamics in relation to the key hazard endpoints which include reproductive and developmental toxicity. Dose-response analyses that were performed using benchmark dose modeling in the previous assessment of NMP use in paint and coating removal (U.S. EPA, 2015) were incorporated where appropriate (see Section 3.2.5). Additional benchmark dose modeling was conducted for the current risk evaluation to include data on reproductive toxicity that was previously unavailable to EPA.

Studies that met the evaluation criteria and were rated low, medium, or high were considered for hazard identification and dose-response analysis as described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). EPA has not developed data quality criteria for all types of hazard

information such as toxicokinetic data; however, this information is used to support the NMP risk evaluation.

Studies considered PECO relevant that scored acceptable in the systematic review data quality evaluation and contained adequate dose-response information were considered for derivation of points of departure (PODs). EPA defines a POD as the dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on the extrapolated dose for an estimated incidence, a change in response level from a dose-response model (e.g., benchmark dose or BMD), a NOAEL value, a lowest-observed-adverse-effect level (LOAEL) for an observed incidence, or a change in the level (i.e., severity) of a given response. PODs were adjusted as appropriate to conform to the specific exposure scenarios evaluated.

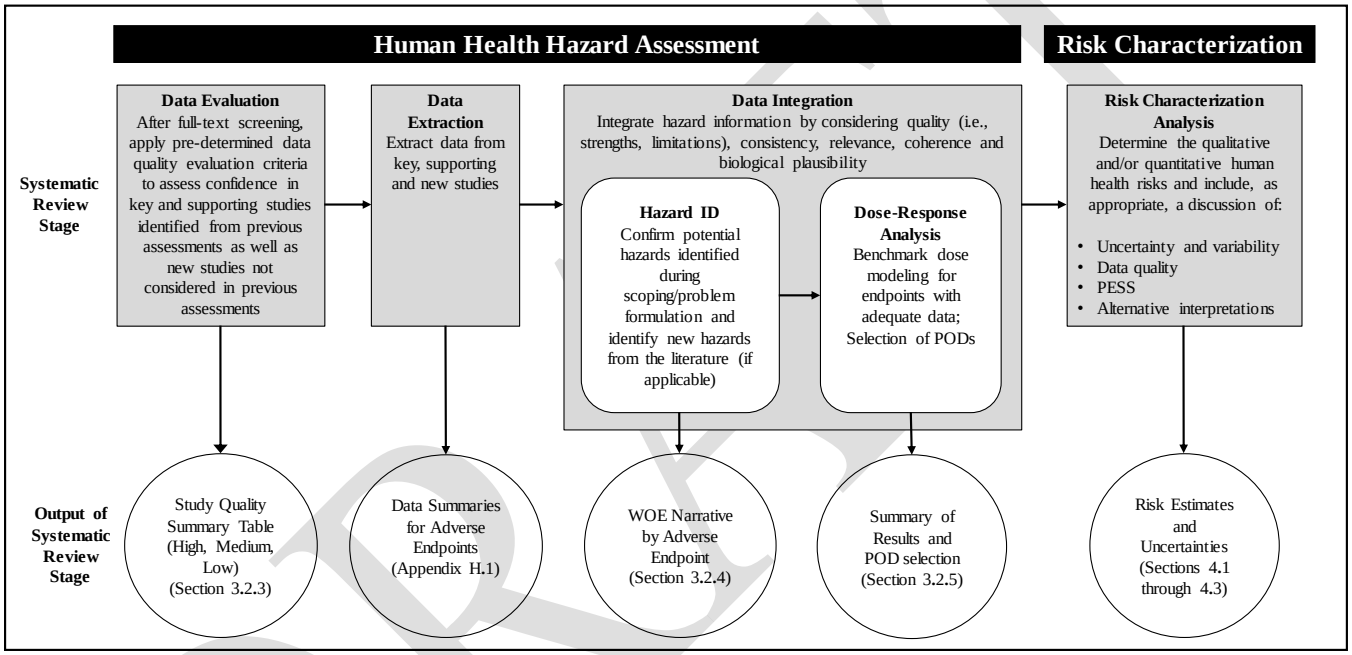


Figure 3-1. Summary of NMP Systematic Review

3.2.2 Toxicokinetics

NMP is readily absorbed by all routes with widespread distribution via the systemic circulation and extensive first pass metabolism to polar compounds that are excreted primarily in urine (Akesson et al., 2004; Ligocka et al., 2003; Akesson and Paulsson, 1997). The major metabolites of NMP in humans are 5-hydroxy-N-methyl-2-pyrrolidone (5-HNMP) and 2-hydroxy-N-methylsuccinimide (2-HMSI); minor metabolites include N-methyl-succinimide (MSI). Over 80% of the administered dose is excreted within 72 hours (Akesson et al., 2004; Akesson and Paulsson, 1997).

Dermal contact with NMP liquids generally presents the greatest potential for human exposure; however, vapor-through skin uptake has also been demonstrated in humans (Akesson et al., 2004; Jönsson and Akesson, 2003). Bader et al. (2008) exposed human volunteers to an NMP air concentration of 80 mg/m^3 for 8 hours and estimated peak concentrations following dermal-only exposure to be in the range of 36 to 42% of the results obtained after whole-body exposure based on NMP equivalents in urine (See Section 3.2.5.5).

3.2.3 Hazard Identification

Previous assessments (EC, 2016; Danish Ministry of the Environment, 2015; U.S. EPA, 2015; NICNAS, 2013; OECD, 2009b; U.S. EPA, 2006b; WHO, 2001) have identified reproductive and developmental toxicity as the most sensitive effects of NMP. EPA therefore focused this risk evaluation on reproductive and developmental effects. This section summarizes evidence for reproductive and developmental hazards as well as a broader range of potential non-cancer and cancer health hazards.

A comprehensive set of summary tables which includes all endpoints considered for this assessment may be found in Appendix H. EPA reviewed the available data and key and supporting studies were evaluated for consistency and relevance to humans, according to the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). The results of the data quality evaluation for the non-cancer studies (key and supporting studies and new studies) are described below in Section 3.2.3.1 and included in the data quality evaluation tables in the *Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019m).

3.2.3.1 Non-Cancer Hazards

Toxicity following Acute Exposure

The acute toxicity of NMP is low based on results from studies conducted via oral, dermal, inhalation, intraperitoneal and intravenous exposure in rats and mice (RIVM, 2013; OECD, 2007b; WHO, 2001). Oral LD_{50} values ranged from 3605 to 7725 mg/kg-bw, dermal LD_{50} values ranged from 5000 to 7000 mg/kg-bw and the 4 hr LC_{50} was > 5100 mg/m^3 (RIVM, 2013). Sublethal effects observed in response to single high doses include body weight gain in rats exposed to 5.1 mg/L of a vapor/aerosol mixture, and ataxia and diuresis in rats exposed orally to 1/8 of the LD_{50} (OECD, 2007).

Irritation and Sensitization

NMP is a skin, eye and respiratory irritant (RIVM, 2013; WHO, 2001). For example, a rabbit 28-day dermal exposure study with rabbits exposed to 413, 826, or 1653 mg/kg/day once a day, five days a week for four weeks resulted in local skin irritation at all doses tested (OECD, 2007b; WHO, 2001). Rabbits receiving a single application of 0.1 ml NMP to one eye experienced corneal opacity, iritis, and conjunctivitis. Effects were reversible within 14 days (OECD, 2007). Nasal irritation (crust formation on nasal edges) was observed in rats exposed to 1, or 3 mg/L for 6 hours a day five days a week for three months. The inhalation study identified a NOAEC of 0.5mg/L (BASF AG, 1994, as cited by OECD, 2007).

Human volunteer chamber studies revealed some discomfort during exposure but are otherwise suggestive of humans being less sensitive to NMP irritation than rodents (RIVM, 2013). Workers exposed to NMP dermally experienced skin irritation (Leira 1992 as cited by (OECD, 2007b)). No respiratory irritation was reported in workers and volunteers exposed via inhalation to up to 50mg/m3 for 8 hours ((Akesson and Jönsson, 1997); NMP Producers Group 2005 as cited by (OECD, 2007b). NMP is not corrosive. Although, available results suggest NMP is not a sensitizer (RIVM, 2013) data are too limited to draw conclusions on sensitization.

Neurotoxicity

A small number of studies noted effects related to neurotoxicity. A RIVM report highlights a 90-day oral repeat dose study in rats with a neurotoxicity screening panel that identified NOAELs of 169 and 217 mg/kg-bw/day for males and females, respectively, based on decreased body weight in both males

and females and reversible neurological effects (including increased foot splay and low arousal) in males only (RIVM, 2013; Malley et al., 1999).

In a rat study, whole body exposure to 0.1, 0.5, and 1.0 mg/L (25, 125, or 250 ppm, aerosol) 6 hours/day five times a week for four weeks was associated with lethargy and irregular respiration at all concentrations. These signs were reversible within 30-45 minutes following exposure at the two lower concentrations. Rats in the highest dose group had excessive mortality. Lethargy and irregular respiration were not reversed in most surviving animals in the high dose group 18 hours after exposure had ceased (Lee et al., 1987). The actual exposure concentrations in this study cannot be determined due to aerosol formation and condensation.

In a gestational exposure study by Lee et al. (1987) rats were exposed to an NMP aerosol concentration of 100 and 360 mg/m^3 (analytical) for six hours/day from GD 6 through 15. Sporadic lethargy and irregular respiration were observed in treated dams at both exposure levels during the first three days of exposure. These effects were not seen during the remainder of the exposure period or during the 10-day recovery period.

Developmental neurotoxicity endpoints have also been evaluated. Hass et al. (1994) investigated the effects of NMP on postnatal development and behavior in rats exposed during gestation. Dams were exposed by whole-body inhalation to measured levels of 151 ppm (612 mg/m^3) for six hrs/day from GD 7 to 20 and offspring were evaluated for a range of growth, development, and neurobehavioral endpoints from PND1 through 7 months of age. Performance was impaired in certain more complex tasks (i.e., reversal procedure in Morris water maze and operant delayed spatial alternation). The impaired performance may be associated with decreased body weight at weaning. As the authors noted, the effect appeared most pronounced in offspring with the lowest body weights in the litter at weaning. Since only one dose was used, a NOAEL could not be established. This study was excluded by the systematic review process and did not go through data quality evaluation because it only used a single dose. It is discussed here because it was cited as a supporting study in a previous EPA assessment (U.S. EPA, 2015), and it provides information about neurodevelopmental endpoints that have not been evaluated in any other studies.

Liver Toxicity

A chronic oral exposure study reported effects on the liver following oral exposure to NMP in rats and mice. Chronic oral exposure in rats was associated with centrilobular fatty change in the liver in males but not in females. This study identified a LOAEL of 678 mg/kg/day and a NOAEL of 207 mg/kg for liver toxicity in male rats (Malley et al., 2001). In mice, significantly increased liver weights as well as cellular alterations in the liver were reported in both male and female mice following oral exposure. The authors reported a LOAEL of 173 mg/kg/day and NOAEL of 89 mg/kg/day for liver toxicity in male mice (Malley et al., 2001). A sub-chronic 90-day oral exposure study in rats and mice at higher doses found no effect on the liver (Malley et al., 1999) while a four-week oral exposure study found increased incidence of centrilobular hepatocellular hypertrophy in addition to increase serum total protein and albumin in female rats exposed to 2268 mg/kg/day (Malek et al., 1997).

Kidney Toxicity

Chronic progressive nephropathy was reported in male but not female rats following chronic oral exposure to 678 mg/kg-bw/day (Malley et al., 2001). No kidney toxicity was observed in male or female

mice in this study (Malley et al., 2001). The study identified a NOAEL of 207 mg/kg/day based on kidney toxicity in male rats. Another study evaluated renal endpoints following four weeks of oral exposure in mice. Dark yellow urine was observed in all animals at 2970 and 4060 mg/kg-bw/day. Cloudy swelling of the distal renal tubule was observed in 3/5 females at 4060 mg/kg-bw/day. This study identified a NOAEL for renal effects of 920 mg/kg-bw/day in females and 720 in males (BASF, 1994). A separate oral exposure study in which male rats received 500 mg/kg/day five days a week for five weeks reported decreased creatinine. The NOAEL for decreased creatinine in male rats this study was 250 mg/kg/day (Gopinathan et al., 2013). This study also reported observations of mottled kidneys in treated rats at all doses, but a lack of incidence data for this endpoint in each dose group prevents identification of a NOAEL or LOAEL for renal effects.

Immune Toxicity

A whole-body inhalation study in rats, which likely included dermal and oral uptake through grooming, identified bone marrow hypoplasia, necrosis of lymphoid tissue in the thymus, spleen and lymph nodes, as well as mortality at the highest dose (RIVM, 2013). The NOAEC for immune effects and for other systemic effects in this study was 500 mg/m^3 (RIVM, 2013; OECD, 2007b). In a four-week oral exposure study, thymic atrophy was observed in female rats exposed to 2268 mg/kg-bw/day. The NOAEL for thymus effects in this study was 1548 mg/kg/day (Malek et al., 1997).

Developmental Toxicity

There is robust evidence of developmental toxicity in animals exposed to NMP. Developmental inhalation, oral and dermal exposures to NMP have been linked to a range of developmental effects, including decreased fetal and pup weights and increased fetal and pup mortality (Sitarek et al., 2012; NMP Producers Group, 1999a; Hass et al., 1994), skeletal malformations, and incomplete skeletal ossification (Saillenfait et al., 2002; DuPont, 1990; Becci et al., 1982). Most of the available developmental toxicity studies for NMP were performed in rats. OECD and RIVM assessments also describe rabbit developmental studies that reported developmental toxicity, including increased resorptions and fetal malformations following gestational exposure to NMP in rabbits (RIVM, 2013; OECD, 2007b).

Effects on postnatal neurological behavior were reported following whole-body inhalation exposure to 151 ppm (612 mg/m^3) NMP during gestation (Hass et al., 1994). However, because behavioral effects were only evaluated at this single exposure level, no NOAEL has been identified for developmental neurotoxicity and dose-response for this endpoint cannot be characterized.

Evidence of developmental toxicity and dose-response information from studies identified as acceptable in the systematic review process is summarized in Table 3-2 and discussed in depth in Sections 3.2.4 and 3.2.5.

Reproductive Toxicity

Reproductive toxicity endpoints that have been observed following repeated exposure to NMP include reduced male fertility and female fecundity and testicular histopathology. Evidence of reproductive toxicity is inconsistent across studies. For example, three oral exposure studies in rats, including a paternal exposure study, a maternal exposure study, and a two-generation study in both sexes (Sitarek et al., 2012; Sitarek and Stetkiewicz, 2008; Exxon, 1991) report reduced male and/or female fertility in response to NMP. Three other two-generation studies in rats failed to identify any effect on fertility. Two of these studies are two-generation dietary exposure studies in rats (NMP Producers Group, 1999a,

b) with dose levels and study designs similar to the Exxon (1991) study. EPA does not have complete access to the data from these studies and is therefore unable to assess data quality. The third study is a two-generation whole-body inhalation exposure study (Solomon et al., 1995) that deviates substantially from EPA and OECD guidelines. In addition, several oral exposure studies have reported effects on testicular histopathology in male rats (Sitarek and Stetkiewicz, 2008; Malley et al., 2001; Malek et al., 1997), while several others find no effect (Malley et al., 1999; Becci et al., 1983; DuPont, 1982).

Evidence of reproductive toxicity is summarized in
Table 3-3 and discussed in depth in Sections 3.2.4 and 3.2.5. Reproductive toxicity findings are challenging to interpret due to the wide-ranging effect levels and the lack of consistency in findings across studies. While developmental effects are more consistently reported across studies, reductions in fertility have been reported at lower doses than developmental effects following repeated exposures.

Table 3-2. Acceptable Studies Evaluated for Developmental Effects

Data Source	Study Description	Effects reported; POD	Data Quality Rating
Oral Exposure Studies			
(Sitarek and Stetkiewicz, 2008)	Oral gavage exposure (0, 100, 300, 1000 mg/kg-bw/day) 5 days/week for 10 weeks in male rats before mating and for one week during mating	Reduced viability of offspring in first four days of life following paternal exposure to 300 mg/kg/day; NOAEL = 100 mg/kg-bw/day	High
(Sitarek et al., 2012)	Oral gavage exposure (0, 150, 450, 1000 mg/kg-bw/day) for 5 days/week for 2 weeks in female rats prior to mating, during mating, gestation and lactation	Number of live pups was reduced at 1000mg/kg-bw/day; Pup survival decreased in all exposure groups; LOAEL for pup survival = 150 mg/kg-bw/day	High
(Saillenfait et al., 2002)	Oral gavage exposure (0, 125, 250, 500, 750 mg/kg-bw/day) through gestational days (GD) 6-20 in rats	Increased resorptions/ post-implantation losses and increased skeletal malformations; NOAEL for developmental effects = 125 mg/kg-bw/day; NOAEL for maternal toxicity = 250 mg/kg-bw/day	High
(Exxon, 1991)	Two-generation oral dietary exposure (50, 160, 500 mg/kg-bw/day) in male and female rats exposed prior to mating, throughout gestation and lactation	Reduced pup survival and growth at 500 mg/kg-bw/day; NOAEL for developmental effects = 160 mg/kg-bw/day	High
(Exxon, 1992)	Oral gavage exposure (40, 125, 400 mg/kg-bw/day) through GD 6-15 in rats	Reduced fetal body weights, reduced ossification sites in proximal phalanges of the hindpaw, and reduced maternal body weight gain at 400 mg/kg-bw/day; NOAEL for maternal and developmental effects = 125 mg/kg-bw/day	High

Data Source	Study Description	Effects reported; POD	Data Quality Rating
Inhalation Exposure Studies			
(Saillenfait et al., 2003)	Inhalation exposure (0, 122, 243, 487 mg/m^3) for 6 hours/day on GD 6-20 in rats	Reduced maternal weight gain and food consumption at 243 mg/m^3; Reduced fetal weight at 487 mg/m^3 exposure; NOAEL for maternal effects= 122 mg/m^3; NOAEL for developmental effects= 243 mg/m^3	High
(Solomon et al., 1995; DuPont, 1990)	Inhalation exposure (0, 42, 206, 472 mg/m^3) for 6 hours/day throughout mating period (100 exposure days) in male rats, and throughout gestation and weaning, except GD 20 – PND 4 (143 exposure days) in females	Decreased fetal body weights and decreased offspring weights; decreased maternal response to auditory stimulus at the highest dose; NOAEL for maternal and developmental effects = 206 mg/m^3	High
(Lee et al., 1987)	Inhalation exposure (100 or 360 mg/m^3) for 6 hours/day on gestational days 6-15 in rats	No effects reported on uterine or litter parameters, fetal weight or length, or incidence of gross, soft tissue, or skeletal anomalies; NOAEL for maternal and developmental effects = 360 mg/m^3	Medium
Dermal Exposure Studies			
(Becci et al., 1982)	Dermal exposure (75, 237, 750 mg/kg-bw/day) on gestational days 6-15 in rats	Decreased number of live fetuses per dam, increased percentage of resorption sites and skeletal abnormalities as well as maternal toxicity indicated by reduced body weight gain at the highest dose; NOAEL = 237 mg/kg-bw/day	Medium

Table 3-3. Acceptable Studies Evaluated for Reproductive Effects

Data Source	Study Description	Effects reported; POD	Data Quality Rating
Oral Exposure Studies			
(Sitarek and Stetkiewicz, 2008)	Oral gavage exposure in male rats (0, 100, 300, 1000 mg/kg-bw/day) 5 days/week for 10 weeks prior to mating and for one week during mating	Male infertility, damage to seminiferous epithelium and significant reduction in thyroid weight at 1000 mg/kg-bw/day; NOAEL for male reproductive effects = 300 mg/kg-bw/day	High
(Sitarek et al., 2012)	Oral gavage exposure (0, 150, 450, 1000 mg/kg-bw/day) for 5 days/week for 2 weeks in female rats prior to mating, during mating, gestation and lactation	Significant reduction in female fertility index at 450 or 1000 mg/kg-bw/day; NOAEL for female fertility = 150 mg/kg-bw/day	High

Data Source	Study Description	Effects reported; POD	Data Quality Rating
(Exxon, 1991)	Two-generation oral dietary exposure (50, 160, 500 mg/kg-bw/day) in male and female Sprague-Dawley rats exposed prior to mating, throughout gestation and lactation	Reduced male fertility and female fecundity in second generation rats (exposed throughout development and prior to mating) at all doses; LOAEL= 50 mg/kg-bw/day; NOAEL not identified	High
(Becci et al., 1983)	Oral dietary exposure (0, 24, 75, 246 mg/kg-bw/day in males; 0, 24, 76, 246 mg/kg-bw/day in females) for 13 weeks in male and female beagle dogs	No effects on reproductive organ weights; NOAEL for reproductive effects = 246 mg/kg-bw/day	High
(Malek et al., 1997)	Oral dietary exposure (0, 2000, 6000, 18000 or 30,000 ppm; 0, 149, 429, 1234, 2019 mg/kg-bw/day) for four weeks in male rats	Decreased body weight and altered testes and liver weights observed at 1234 mg/kg-bw/day and above. Degeneration/atrophy of testicular seminiferous tubules were observed 1/5 males at 1234 mg/kg-bw/day and in 5/5 at 2019 mg/kg-bw/day; NOAEL for reproductive effects = 429 mg/kg-bw/day	High
(Malley et al., 1999)	Oral dietary exposure (0, 3000, 7500 or 18,000 ppm) for 90 days in male rats (0, 169, 433, 1057 mg/kg-bw/day) and female rats (0, 217, 565, 1344 mg/kg-bw/day); oral dietary exposure (0, 1000, 2500, or 7500 ppm) for 90 days in mice (0, 277, 619, 1931 mg/kg-bw/day)	No effect on reproductive organ weights. NOAEL in rats = 1057 mg/kg-bw/day; NOAEL in mice = 1931 mg/kg-bw/day	High
(Malley et al., 2001)	Chronic dietary oral exposure in rats (0, 1600, 5000 or 15,000 ppm) for two years (0, 66.4, 207, 678 mg/kg-bw/day in male rats), (0, 87.8, 283, 939 mg/kg-bw/day in female rats) and dietary exposure (0, 600, 1200 or 7200 ppm) for 18 months in mice (0, 89, 173, 1089 mg/kg-bw/day in male mice) and (0, 115, 221, 1399 mg/kg-bw/day in female mice)	In male rats only, bilateral degeneration/atrophy of seminiferous tubules in the testes, and bilateral oligospermia/germ cell debris in the epididymis at the highest dose; NOAEL for male reproductive effects = 207 mg/kg-bw/day	High

Data Source	Study Description	Effects reported; POD	Data Quality Rating
(BASF, 1994)	Oral dietary exposure (0, 500, 2500, 7500 or 10,000 ppm; 130, 720, 2130, 2670 mg/kg-bw/day) for four weeks in male mice	No exposure related reproductive organ effects reported; NOAEL for reproductive effects in mice = 2670 mg/kg-bw/day	High
Inhalation Exposure Studies			
(Solomon et al., 1995; DuPont, 1990)	Two generation whole body inhalation exposure (0, 42, 206, 472 mg/m^3) for 6 hours/day, 7 days/week throughout mating period, gestation, and weaning in male and female rats	No significant change in indices of reproductive performance (fertility and fecundity); NOAEL for reproductive effects = 472 mg/m^3	High
(DuPont, 1982)	Chronic whole-body inhalation exposure (0, 41, 405 mg/m^3) 6 hours/day, 5 days/week for two years in male and female rats	Mammary gland hyperplasia; No adverse effects reported based on histopathology of the epididymis and prostate. NOAEL for mammary gland effects = 10 ppm (41 mg/m^3); NOAEL for male reproductive effects = 100 ppm (405 mg/m^3))	Medium

3.2.3.2 Genotoxicity and Cancer Hazards

3.2.3.2.1 Genotoxicity and Other Mechanistic Data

EPA has reviewed summaries of the unpublished genotoxicity studies identified below and has contacted the data owners to obtain full studies. Although EPA did not evaluate the genotoxicity and mechanistic studies using updated data quality criteria presented in Application of Systematic Review in TSCA Risk Evaluations (U.S. EPA, 2018a), all studies are considered acceptable (e.g., conduct of the studies, use and proper response of positive controls) as presented at the international OECD meeting (SIAM 24) and publication in the Screening Information Assessment Report and Dossier (OECD, 2007b). One study considered to be invalid within OECD (2007b) is also described below.

In Vivo Genotoxicity Studies

NMP has been evaluated for potential genotoxicity in several in vivo studies, summarized in Table 3-4. NMP was examined for its clastogenic/genotoxic potential in vivo in the Chinese hamster cytogenic assay and administered once daily by gavage in doses of 1,900 and 3,800 mg/kg bw/day. NMP treatment led to signs of systemic toxicity but did not result in increased numbers of mitotic cells containing structural chromosomal alterations or numerical chromosomal aberrations. An earlier screening study also showed no clastogenic potential of NMP in vivo after whole body inhalation of 800 ppm (measured value of 1,750 mg/m^3) for 6 hrs/day, 5 days/week for 6 weeks (BASF AG, 1976d) as cited in OECD (2007b).

In a mouse bone marrow micronucleus test, NMP was dissolved in distilled water and administered to NMRI mice once daily by gavage at 950, 1,900 and 3,800 mg/kg bw/day. NMP treatment led to clinical signs of toxicity, including irregular respiration, abdominal position and poor general state. NMP did not induce micronuclei in the polychromatic erythrocytes of mice treated up to a dose showing clinical signs

of toxicity and bone marrow toxicity. No indication of a spindle poisoning effect was detected (BASF AG, 1989c) as cited in OECD (2007b) and Engelhardt and Fleig (1993).
NMP did not show mutagenic activity in germ cells in a dominant lethal test in male NMRI mice after intraperitoneal treatment with a single dose of 393 mg/kg bw/day (380 µl/kg bw; BASF AG, 1976a; Roehrborn and Vogel, 1967) as cited in OECD (2007b).

Table 3-4. Summary of In Vivo Genotoxicity Studies

Study Type	Dose level/ Concentration	Result	Remark	Reference
Cytogenetic assay, Chinese hamster	1900, 3800 mg/kg bw/day oral (gavage), single application	negative	Signs of systemic toxicity	Engelhardt and Fleig, 1993
Cytogenetic assay, Chinese hamster	3,244 mg/m^3 inhalation (whole body), 6 h(day, 5x/week, 6 weeks (28 exposures),	negative	Whole body exposure	BASF AG, 1976d
Micronucleus assay, Mouse (NMRI)	0, 950, 1900, 3800 mg/kg bw/day oral (gavage), single application	Negative, no indication of a spindle poisoning effect	Signs of systemic and bone marrow toxicity	BASF AG, 1989c; Engelhardt and Fleig, 1993
Dominant lethal assay, Mouse (NMRI)	0, 393 mg/kg single i.p.,	negative	No mutagenic activity in germ cells	BASF AG, 1976a; Roehrborn and Vogel, 1967
Source: OECD (2007b), Table 9, p. 32; all references are cited in OECD (2007b)				

In Vitro Genotoxicity Studies

In vitro studies evaluating potential genotoxicity of NMP are summarized in Table 3-5. NMP was tested for mutagenicity in the Ames test on bacteria both with and without metabolic activation. The Salmonella typhimurium strains TA 98, TA 100, TA 1535 and TA 1537 were exposed to the test substance at concentrations ranging from 3.15 to 30,000 nl/plate. NMP was not mutagenic in the Ames test under the experimental conditions used (BASF AG, 1978a) as cited in OECD (2007b). Wells (1988) evaluated NMP in an Ames assay using several *S. typhimurium* strains both with and without metabolic activation. In the assay without activation, increased revertants were observed for TA 102 and TA 104 but the increases were not greater than two times background and showed no clear dose-response relationship. NMP was evaluated in another Ames assay using several *S. typhimurium* strains both with and without metabolic activation and was determined to be negative (Mortelmans et al., 1986).

NMP was evaluated in an HGPRT assay using Chinese hamster ovary cells at concentrations ranging from 0.5 to 5.0 mg/ml (with and without S9 mix) and showed no cytotoxicity and did not increase the mutation rate (GAF Corp., 1988; TSCAT, 1990b) as cited in OECD (2007b). Mayer et al. (1988) reported that NMP induced a dose-related increase in the aneuploidy rate in yeast at concentrations in the range of 154.0 to 229.3 mM. However, OECD (2007b) noted that these dose levels were clearly

cytotoxic in a dose-dependent manner and determined the study to be invalid by stating it was a biological system of little relevance. Furthermore, OECD has deleted test guidelines using yeast because tests for mammalian cells are preferred (OECD, 2017).

In a mouse lymphoma test in the L5178 Y cell line with concentrations of 0, 1,000, 4,000, 8,000 or 10,000 ppm (v/v) without/with S-9 mix, NMP showed good solubility and revealed no cytotoxicity or mutagenic response at any concentration (E.I. du Pont de Nemours and Company, 1976, TSCAT, 1990c[sic]) as cited in OECD (2007b).

NMP was evaluated (to determine its ability to interact with DNA) in an in vitro assay with primary hepatocytes from the liver of an untreated male F-344 rat. Test concentrations ranged from 250 - 5000 µg/ml. NMP was shown to be soluble and slightly cytotoxic at concentrations ≥ 4,000 µg/ml. NMP did not induce significant changes in nuclear labeling of rat primary hepatocytes at concentrations ranging from 500 - 5,000 µg/ml, covering a wide range of cell survival (53.2% - 98.6%; GAF Corp., 1988b; TSCAT, 1990b; Vetline Inc., 1988) as cited in OECD (2007b).

Table 3-5. Summary of In Vitro Genotoxicity Studies

Bioassay Test system	Concentration With/without metabolic activation (+/- S9 mix)	Result	Remark	Reference
Ames test, *S. typhimurium* (TA98, TA100, TA1535, TA1537),	3.15 – 30000 nl/plate (+/- S9 mix)	negative	Standard plate test	BASF AG, 1978a
Ames test, *S. typhimurium* (*TA97*, TA98, TA100, TA1535, TA1537)	0, 100, 333, 1000, 3333, 10000 µg/plate (+/- S9 mix)	negative	Preincuba-tion assay, Compara-tive study within NTP testing	Mortelmans et al., 1986
Ames test, *S. typhimurium* (*TA97*, TA98, TA100, TA102, TA104, TA2638, UTH8413, UHT8414)	0.01 – 1000 µM/plate (+/- S9 mix)	negative	Standard plate test	Wells et al., 1988
Ames test, *S. typhimurium* (TA98, TA104)	0.01 – 1000 µM/plate (+/- S9 mix)	negative	Preincuba-tion assay	Wells et al., 1988
HGPRT test, CHO cells,	0.5 – 5.0 mg/ml (+/- S9 mix)	negative		GAF Corp., 1988; TSCAT, 1990b
Mouse lymphoma assay,	1000 – 10000 ppm (V/V) (+/- S9 mix)	negative		E.I. du Pont de Nemours

Bioassay Test system	Concentration With/without metabolic activation (+/- S9 mix)	Result	Remark	Reference
L5178Y cells,				and Company, 1976; TSCAT, 1990b
UDS, Rat primary hepatocytes,	250 – 5000 µg/ml	negative		GAF Corp., 1988b; TSCAT, 1990b; Vetline Inc., 1988
Source: OECD (2007b), Table 8, pp. 30-31; All references are as cited in OECD (2007b)				

No clastogenic or aneugenic potential of NMP was reported for somatic or germ cells in in vivo studies. For some genetic endpoints examined in vitro (e.g., point mutations, DNA damage and repair), NMP also showed negative responses in several bacterial and mammalian test systems. A positive result for aneuploidy in yeast was determined to be invalid by OECD (2007b).

Other Mechanistic Studies

The effect of NMP on cell proliferation in the liver (S-phase response) after one or four weeks of dietary exposure at 7200 ppm (1392/1906 mg/kg bw/day in males/females) using B6C3F1 mice was investigated. Incorporation of bromodeoxyuridine (BrdU) into liver DNA was examined microscopically. The cell proliferation rate in liver increased 6.9-fold in treated males and 3.3-fold in treated females as compared to untreated control animals. Males (9/10) also exhibited minimal to slight centrilobular hepatocellular hypertrophy as compared to females which showed an incidence of 1/10for this effect.

Males showed a 2.1-fold increase in cell proliferation rate in liver; a 1.7-fold increase was observed in females. An increase in the incidence of apoptotic liver cells was observed in males only, with minimal to slight centrilobular hypertrophy recorded in 7/10 male and 2/10 female mice, respectively. In conclusion, NMP induced increased hepatocellular proliferation after dietary exposure for one or four weeks (NMP Producers Group, 2002b) as cited in OECD (2007b).

NMP was investigated for its ability to induce liver enzymes or peroxisome proliferation in B6C3F1 mice treated at 7200 ppm via the diet (1364/1945 mg/kg bw/day in males/females). This dose was also shown to increase liver tumors in mice. The livers taken from 10 animals per sex were examined for cytochrome P450-content, and enzyme activity (ethoxyresorufin-O-deethylase (EROD) and pentoxyresorufin-O-dependentylase (PROD)). In addition, 5 male and 5 female mice were examined for treatment-related changes in cyanide-insensitive Palmitoyl-CoA-oxidation (PALCoA) and histopathology, including changes in peroxisomes, endoplasmic reticulum or mitochondria. NMP exposure resulted in a slight increase in the activity of PALCoA in male animals; electron microscopy also revealed a slight elevation in peroxisomes in 2/5 males (NMP Producers group, 2002a) as cited in OECD (2007b).

Conclusions

NMP has been evaluated in several in vitro and in vivo genotoxicity assays that cover a range of endpoints, including chromosomal aberration, DNA damage and repair, and point mutations. Negative results in these mammalian and bacterial test systems representing multiple endpoints indicate that NMP is unlikely to be genotoxic.

3.2.3.2.2 Carcinogenicity

In a 2-year inhalation cancer bioassay, Sprague-Dawley rats (120 per sex per concentration) were exposed in a whole-body experiment to NMP vapor concentrations of 41 and 405 mg/m^3 (0, 10 and 100 ppm) for 6 h/day, 5 days/week. Survival of treated rats did not differ from controls. Other than an increase in pituitary adenocarcinomas at 41 mg/m^3 at 18 months but not at 405 mg/m^3 or at 24 months, there were no increases in incidence of benign or malignant tumors at any concentration (Lee et al., 1987; DuPont, 1982).

In an oral dietary study, NMP was examined for its chronic toxicity and carcinogenic potential in groups of 62 male and 62 female Sprague-Dawley rats at concentrations of 0, 1600, 5000 or 15000 ppm (about 66/88, 207/283, 678/939 mg/kg bw/day, males/females) in food for two years. The survival of female rats was not affected, but males in the high dose group had lower survival due to increased severe chronic-progressive nephropathy. The incidence of benign or malignant tumors was not increased among rats (Malley et al., 2001; NMP Producers Group, 1997).

NMP was also administered to groups of 50 male and 50 female B6C3F1 mice receiving dietary concentrations of 0, 600, 1200 and 7200 ppm (about 89/115, 173/221, 1089/1399 mg/kg-bw/day, males/females) in an 18-month study. There was no difference in survival of treated mice compared with controls. Among the 7200 ppm males, incidences of liver carcinomas were increased, whereas the incidence in females was within the historical control range. Increased incidences of liver adenomas were also noted at 7200 ppm; these occurred in both sexes. NMP also caused other substance-related effects in the liver at 1,200 and 7,200 ppm. For example, increased metabolic activity was observed. In addition, mice exhibited increased liver weights and incidences of foci of cellular alteration in the liver at 7200 ppm in both sexes. In the 1200 ppm group, increased liver weights were also observed among males and 3/50 of the mice exhibited centrilobular liver cell hypertrophy (Malley et al., 2001) and NMP Producers Group, 1999a, as cited in OECD (2007b). Results of cancer bioassays for NMP are summarized in Table 3-6.

Table 3-6. Summary of Tumor Incidence Data from Cancer Bioassays

Species/Strain/ Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Cancer Incidence	Effect	Reference	Data Quality Evaluation
Rat/Crj: CD(SD)/ Both (120)	Inhalation, whole body	0, 41, 405 mg/m^3	6 hrs/day 5 days/week for 2 years	Summary data not presented	Increased pituitary adenocarcin-omas at 41 but not 405 mg/m3 and at 18 but not 24 months	DuPont (1982)[a]	Medium
Rat/Other/ Female (62)	Oral, dietary	0, 87.8, 283, 939 mg/kg-bw/day (0, 1600, 5000, 15,000 ppm)	2 years	0, 2, 3, 3	At least one mammary neoplasm	Malley et al. (2001)[b]	High
Mouse/ B6C3F1/ Male (50)		0, 89, 173, 1089 mg/kg-bw/day (0, 600, 1200, 7200 ppm)	18 months	5, 2, 4, 12[c]	Increased incidence of hepatocellular adenoma		
				4, 1, 3, 13[c]	Increased incidence of hepatocellular carcinoma		
Mouse/B6C3F 1/ Female (50)		0, 115, 221, 1399 mg/kg-bw/day (0, 600, 1200, 7200 ppm)		2, 2, 1, 7 [c]	Increased hepatocellular adenoma and carcinoma		
				0, 0, 0, 3 [c]	Increased hepatocellular carcinoma		

[a] This is the unpublished study of the published study identified as Lee et al. (1987)
[b] Unpublished results in rats are available as NMP Producers Group (1997); the unpublished mouse study is NMP Producers Group, 1999a, as cited in OECD (2007b)
[c] $p < 0.05$ by Cochran-Armitage trend test

3.2.4 Weight of Scientific Evidence

The best available human health hazard science was selected for dose-response modeling based on integrating the results of the data evaluation and weight-of-the-scientific evidence. Other recent assessments (EC, 2016; Danish Ministry of the Environment, 2015; U.S. EPA, 2015; NICNAS, 2013; OECD, 2009b; U.S. EPA, 2006b; WHO, 2001) have previously evaluated the weight of scientific evidence and identified reproductive and developmental toxicity as the most sensitive health effects associated with exposure to NMP. This section therefore focuses on the weight-of-the-scientific evidence for reproductive and developmental toxicity for both short-term and chronic exposures.

3.2.4.1 Weight of Scientific Evidence for Developmental Toxicity

A review of the reasonably available information shows comparable effect levels for developmental toxicity, with NOAELs typically ranging from 100-200 mg/kg-bw/day reported in oral exposure studies and effect levels ranging 479-612 mg/m^3 reported in the inhalation exposure studies. EPA identified sensitive and biologically relevant effects that occur along a continuum of reproductive and developmental toxicity, including decreased fetal and pup body weight, delayed ossification, skeletal malformations and increased fetal and pup mortality. These endpoints are discussed in more detail below.

A well-documented case report provides qualitative support for results in laboratory animals indicating that NMP may be detrimental to mammalian development. In this case report, a pregnant woman who was exposed to NMP at work via dermal and inhalation exposure aborted at week 31 of pregnancy. Although the precise exposure levels are unknown, she reportedly cleaned up an NMP spill that dissolved her latex gloves during week 16 of the pregnancy. She was ill for the next four days and experienced malaise, headache, nausea and vomiting (Solomon et al., 1996). Although this study provides some evidence that NMP may harm the developing conceptus, the lack of quantitative exposure data precludes its use for quantitative risk estimation.

Becci et al. (1982) reported adverse developmental effects in Sprague–Dawley rats following NMP exposure via dermal administration. Dams were exposed to NMP at 0, 75, 237 or 750 mg/kg-bw on gestation days (GD) 6-15. All animals were killed and subjected to uterine examination on day 20 of gestation. Treatment at 750 mg/kg-bw was associated with significant decreases in maternal body weight gain, and live litter size, as well as an increased incidence of resorptions and skeletal anomalies. No evidence of teratogenic or maternal effects was observed at 75 or 237 mg/kg-bw; the NOAEL for maternal and developmental toxicity was 237 mg/kg-bw.

Developmental toxicity was reported in Sprague–Dawley rats after NMP exposure via gavage administration (Saillenfait et al., 2002). Pregnant rats were dosed at 0, 125, 250, 500, or 750 mg/kg-bw on GD 6-20. All animals were killed and subjected to uterine examination on day 21 of gestation. A dose-related decrease in fetal body weights (males, females) was observed at all doses, reaching statistical significance at 250 mg/kg-bw. Significantly decreased maternal body weight gain/food consumption and an increased incidence of post implantation loss/fetal resorption and fetal malformations were reported at doses $\geq$ 500 mg/kg-bw; observed treatment-related anomalies included imperforate anus, the absence of a tail and malformation of the spinal column, heart and/or great vessels. The NOAELs for maternal and developmental toxicity were 250 and 125 mg/kg/day, respectively.

The developmental toxicity of NMP was also studied in Sprague–Dawley rats after whole body inhalation exposure (Saillenfait et al., 2003). Pregnant rats were exposed to NMP vapor at 0, 30, 60 or 120 ppm (0, 122, 243 and 487 mg/m^3 nominal concentration), 6 h/day, on GD 6-20. Maternal body weight gain was significantly decreased at 60 and 120 ppm during the first half of exposure (GD 6–13) and maternal food consumption was reduced at 120 ppm on GD 13–21; however, no significant difference in the gestational weight change of treated dams was observed when maternal body weight was corrected for gravid uterine weight. No evidence of teratogenicity was observed at any concentration tested. Fetal toxicity, as evidenced by dose-related decreases in fetal body weight (males, females) was observed at all doses tested, reaching statistical significance at 120 ppm (5-6% reduction in

body weight relative to controls). The NOAEC for maternal and developmental toxicity were 30 and 60 ppm, respectively.

These findings are consistent with reports of fetal growth retardation and the absence of teratogenic effects in previous studies of the developmental toxicity of inhaled NMP. In a two-generation reproduction study, Sprague Dawley rats were exposed to NMP via (whole body) inhalation at 116 ppm, 6 h/day, prior to mating and throughout gestation and lactation (Solomon et al., 1995). Half of the dams were subjected to cesarean section on GD 21 and the remaining litters were evaluated up to weaning. No adverse effects on offspring viability or morphology were reported other than a decrease in fetal and pup body weights. Hass et al. (1995) exposed pregnant rats via (whole body) inhalation to 165 ppm NMP, 6 h per day, from GD 4-20. Delayed skeletal ossification and decreased fetal body weights were reported in offspring of treated dams following NMP exposure. In a previous study, (whole body) inhalation exposure to Wistar rats at 150 ppm NMP on GD 7–20 resulted in significantly decreased pup body weights that persisted from birth until 5 weeks of age. No signs of maternal toxicity were observed in either study (Hass et al., 1994).

Mortality and structural malformations have been detected in rats following high levels of NMP exposure via dermal (Becci et al., 1982) and gavage administration (Saillenfait et al., 2002). Differences in the developmental response to NMP may be ascribed in part, to quantitative and/or qualitative differences in the exposure of the embryo/fetus by route of administration. Studies in humans and rats indicate that NMP is readily absorbed by all routes of exposure and extensively metabolized prior to excretion in urine; however, the peak concentration and residence time of the parent compound may vary depending on the route of exposure and the metabolic "status" of the exposed individual (Jönsson and Akesson, 2001; 2000; Anundi et al., 2000; Akesson and Jönsson, 1997; Ursin et al., 1995; Midgley et al., 1992).

NMP and its metabolites were evaluated for potential embryotoxicity using the rat whole embryo culture (WEC) and the BALB/c 3T3 cytotoxicity test (Flick et al., 2009). The resulting data were evaluated using two strategies; one based on all endpoints evaluated in the WEC and the other included endpoints from both the WEC and a cytotoxicity test. Based on the reported results, the substance with the highest embryotoxic potential was NMP, followed by 5-hydroxy-N-methyl-pyrrolidone (5-HNMP), 2-hydroxy-N-methylsuccinimide (2-HMSI) and N-methylsuccinimide (MSI). Developmental anomalies induced by NMP and 5-HNMP include aberrations in the head region of the embryos, abnormal development of the second branchial arches and open neural pores. Only NMP and 5-HNMP induced specific embryotoxic effects, whereas the other two metabolites, 2-HMSI and MSI, were determined to be non-embryotoxic.

EPA assessed risks for adverse developmental effects within the context of the exposure scenarios identified in the exposure assessment, as summarized in Table 3-7.

3.2.4.1 Weight of Scientific Evidence for Reproductive Toxicity

A review of the reasonably available scientific information identified decreased male and female fertility and testicular lesions and atrophy as potential reproductive effects of NMP exposure. Effects on fertility have been reported at doses lower than those associated with developmental effects, but are less consistently observed across studies than developmental effects.

Three oral exposure reproductive studies reported reduced fertility or reproductive success. Sitarek et al. (2012) reported a decrease in the number of pregnant female rats following oral gavage exposure to 450 mg/kg-bw/day five days a week for two weeks prior to mating. This study identified a NOAEL of 150 mg/kg-bw/day for reproductive toxicity. Another study focused on effects of paternal exposure via oral gavage. Paternal NMP exposure for ten weeks prior to mating and during mating was associated with reduced male fertility (NOAEL = 300 mg/kg-bw/day) and decreased viability of offspring in the first four days of life (NOAEL = 100 mg/kg-bw/day) (Sitarek and Stetkiewicz, 2008).

In a two-generation study, Exxon Biomedical Sciences (1991) reported significant decreases in male fertility and female fecundity as well as reduced survival and growth rates in offspring following oral dietary exposure to 500 mg/kg/day beginning ten days prior to conception and throughout gestation and lactation. In the second generation (rats exposed throughout development and as adults during mating), significant reductions in male fertility and female fecundity were reported at all doses. At 50 mg/kg-bw/day, the lowest dose tested, male fertility decreased 18-28% and female fecundity decreased 18-20% relative to controls. Study authors concluded that these statistically significant effects were not biologically significant at low and mid-range doses because they were "within or close to historical control ranges" and identified a NOAEL of 160 mg/kg-bw/day for reproductive effects. However, historical control data from the performing laboratory were not provided. EPA considered these significant reductions in male fertility and female fecundity relative to concurrent controls biologically relevant and identified the lowest dose tested, 50 mg/kg/day, as the LOAEL for reproductive effects.

In reviewing the findings from Exxon (1991), EPA also considered limited published historical control data (HCD) for Sprague-Dawley rat male and female fertility in reproductive toxicity studies, as well as available online information from a contract research laboratory (CRO) (Charles River, 2018). These sources reported mean male HCD fertility indices of 86.4% in second generation males from 27 reproduction studies (Marty et al., 2009, 1580376) and 94.1% from 208 studies (4359 rats) assessed by the CRO (Charles River, 2018). Mean female HCD fertility indices were 87.5% in second generation females from 27 studies reported by Marty et al. (2009), and 93.9% from 211 studies (4854 rats) evaluated by the CRO. These data support the EPA interpretation of the Exxon (1991) fertility data, although it is acknowledged that appropriate HCD data from the performing laboratory are preferred for use in data interpretation (U.S. EPA, 1991c).

Other two-generation studies did not replicate effects on reduced fertility. Two two-generation guideline dietary exposure studies in rats reported no adverse reproductive effects at the highest doses tested (500 mg/kg/bw/day, subsequently reduced to 350 mg/kg-bw/day due to pup mortality) (NMP Producers Group, 1999a, b). EPA has reviewed summaries of these two unpublished two-generation studies (RIVM, 2013; OECD, 2007b) but data in these reports are not publicly available and EPA does not have complete access to the full reports. EPA is therefore unable to evaluate study quality or incorporate quantitative information from these studies into the dose-response assessment. A two-generation whole body inhalation exposure study in rats also found no effects on fertility or fecundity following exposure to 10, 51, or 116 ppm NMP for 6 hr/day, 7 days/week prior to mating, and during mating, gestation, and lactation (Solomon et al., 1995). However, the second-generation rats were not exposed from weaning to mating, and the F1 adults were mated with a cohort of untreated rats. In addition, there were uncertainties related to actual exposures achieved in this study.

Several oral repeated-dose studies detected testicular lesions and smaller testes (atrophy). A four-week oral exposure study identified a NOAEL of 429 mg/kg-bw/day for testicular lesions and atrophy (Malek et al., 1997) while a two-year oral exposure study in rats identified a NOAEL of 207 mg/kg/day for testicular lesions and atrophy (Malley et al., 2001). The same study observed no effect on testicular atrophy in mice. In a third oral exposure study, male mice were exposed to NMP for ten weeks prior to mating and during mating. This study reported cellular depletion of seminiferous tubule epithelium and reduced male fertility at 1000 mg/kg-bw/day, but not at 300 mg/kg-bw/day (Sitarek and Stetkiewicz, 2008).

Other studies reported no effect on male reproductive endpoints, including a three month oral exposure in beagle dogs (NOAEL = 246 mg/kg-bw/day) (Becci et al., 1983) and a 90 day oral exposure study in rats (NOAEL = 1057 mg/kg-bw/day) and mice (NOAEL = 1931 mg/kg-bw/day) (Malley et al., 1999) and a chronic inhalation study in rats (NOAEL= 100 mg/kg-bw/day) (DuPont, 1982).

EPA assessed risks for adverse reproductive effects within the context of the exposure scenarios identified in the exposure assessment, as summarized in Table 3-7.

Table 3-7. Summary of Exposure Pathways and Toxicity Endpoints used for Risk Evaluation

Receptors	Exposure Pathway and Analytical Approach	
	Acute Dermal and Inhalation Exposures	**Chronic Dermal and Inhalation Exposures**
Worker Users and Nearby Worker Non-Users	Toxic endpoint: Developmental toxicity [a] Risk approach: Margin of Exposure (MOE)	Toxic Endpoint: Reproductive toxicity (fertility/developmental) Risk approach: Margin of Exposure (MOE)
Consumer Users and Nearby Residential Non-Users		Chronic risks were not evaluated. This pathway was not expected to occur in consumer users or bystanders.
[a] Acute dermal and inhalation toxicity studies were not used because they typically measure lethality at high doses and do not provide the level of analysis to assess non-effect levels from single exposures.		

3.2.5 Dose-Response Assessment

This section identifies the endpoints EPA selected for risk estimation. Available studies were reviewed based on study design, analysis and reporting quality to evaluate their individual strengths and weaknesses as summarized in Section 0. Guideline studies and other protocols that utilized good laboratory practices were considered if they met PECO and study quality criteria. The selected studies were then evaluated in the dose-response assessment.

Effects observed in multiple studies that were determined to be sensitive and biologically relevant, were considered for points of departure (POD) and dose-response analysis. These endpoints include:

- Decreased fetal/pup weight, PND 0, 4, 21
- Increased fetal/pup mortality, PND 0, 4, 21
- Skeletal malformations and incomplete skeletal ossification
- Reduced male and female fertility

Although it is unclear whether fetal effects are secondary to maternal toxicity, NMP can cross the placenta (RIVM, 2013); therefore, EPA considers the fetal effects observed following NMP exposure to be biologically relevant.

Numerous studies are available to assess the developmental effects of NMP exposure in rats. Most are based on oral exposure, although some administered NMP via inhalation route. One study evaluated the developmental effects following dermal exposure to rats. Table 3-8 summarizes the developmental endpoints evaluated in the studies reviewed for this assessment. Although developmental outcomes may vary due to temporal variations in vulnerability, EPA considers the general consistency of outcomes observed across different species, routes, durations and windows of exposure to be supportive of the robustness of this treatment effect.

Several studies are available to assess the reproductive effects of NMP exposure. While reproductive effects are less consistently reported across studies than developmental effects, reduced fertility following exposure throughout gestation, lactation, growth, puberty, and prior to mating is a particularly sensitive endpoint. It is consistent with reduced fertility observed at higher doses following exposure to NMP prior to mating. Table 3-9 summarizes the effects on fertility observed in studies considered in this assessment.

Table 3-8. Evidence for NMP-induced Developmental Toxicity

	Study	Data Quality Score	Fetal Weight GD 20 - PND 1	Pup Weight PND 4	Pup Weight PND 21	Fetal Mortality [a] (multiple metrics)	Pup Mortality PND 4	Pup Mortality PND 21	Incomplete Ossification	Skeletal Malformations
ORAL STUDIES	(Sitarek et al., 2012)	High	--	↓	↓	↑	↑	↑	**NA**	**NA**
	(Sitarek and Stetkiewicz, 2008)	High	**NA**	**NA**	**NA**	--	↑	--	**NA**	**NA**
	(NMP Producers Group, 1999a)[c]	Not rated		↓	↓	↑	↑	↑		
	(NMP Producers Group, 1999b)[c]	Not rated		↓	↓	↑	↑	↑		
	(Saillenfait et al., 2002)	High	↓	**NA**	**NA**	↑	**NA**	**NA**	↑	↑

	Study	Data Quality Score	Fetal Weight GD 20 - PND 1	Pup Weight PND 4	Pup Weight PND 21	Fetal Mortality [a] (multiple metrics)	Pup Mortality PND 4	Pup Mortality PND 21	Incomplete Ossification	Skeletal Malformations
	(Exxon, 1992)	High	↓	**NA**	**NA**	--	**NA**	**NA**	↑	--
INHALATION STUDIES	(Saillenfait et al., 2003)	High	↓	**NA**	**NA**	--	**NA**	**NA**	--	--
	(Hass et al., 1995)[d]	Not rated	↓	**NA**	**NA**	↑	**NA**	**NA**	↑	--
	(Hass et al., 1994)[d]	Not rated	↓	↓	↓	--	--	--	**NA**	**NA**
	(Solomon et al., 1995; DuPont, 1990)	High	↓	↓	↓	↑[b]	--	--	↑	↑
	(Lee et al., 1987)	High	--	**NA**		--	**NA**		--	--
DERMAL STUDIES	(Becci et al., 1982)	Medium	↓	**NA**	↑	**NA**	**NA**	**NA**	↑	↑

↓ indicates decrease, ↑ indicates increase, -- indicates no change
[a] May be based on resorptions, post-implantation loss, dead pups at birth or decreased live pups at birth
[b] Statistically significant increase for p = 0.1
[c] Studies not rated because EPA does not have access to the complete study report. These studies are included here because previous assessments have cited them as supporting studies and they contribute to overall weight of evidence.
[d] Studies not rated because they were excluded by the PECO statement in the systematic review process due to the lack of dose-response information (the study used a single high dose). These studies are included here because previous assessments have cited them as supporting studies and they contribute to overall weight of evidence.
NA = Not Assessed
Blank = Data not publicly available

Table 3-9. Evidence for NMP-induced Reproductive Toxicity

	Study	Data Quality Score	Effects following adult exposure		Effects following exposure throughout development[a]	
			Male fertility	Female fecundity	Male fertility	Female fecundity
ORAL STUDIES	(Exxon, 1991)	High	--	--	↓	↓
	(Sitarek et al., 2012)	High	**NA**	↓	**NA**	**NA**
	(Sitarek and Stetkiewicz, 2008)	High	↓	**NA**	**NA**	**NA**
	(NMP Producers Group, 1999a)[b]	Not available				
	(NMP Producers Group, 1999b)[b]	Not available				
INHALATION STUDIES	(Solomon et al., 1995; DuPont, 1990)	High	--	--	--	--

↓ indicates decrease, ↑ indicates increase, -- indicates no change
[a] In Exxon 1991 and the NMP Producers Group 1999 studies, reproductive effects in the second generation were evaluated following exposures throughout gestation, lactation, growth, puberty and adulthood prior to mating. In the Solomon et al 1995/Dupont 1990 study, second generation rats were not exposed after weaning and exposed rats were mated with unexposed controls.
[b] Studies not rated because EPA does not have access to the complete study reports. These studies are included here because previous assessments have cited them as supporting studies and they contribute to overall weight of evidence.
NA = Not Assessed
Blank = Data not publicly available

3.2.5.1 Selection of Endpoints for Dose-Response Assessment

Decreased fetal/pup weights

Decreased fetal and/or postnatal body weights were consistently observed across studies despite variations in dosing time and exposure routes. The fetal and postnatal body weight effects noted in Table 3-8 were plotted graphically in exposure-response arrays (**Figure 3-2** and Figure 3-3). Exposure-response arrays are a graphical representation of available dose-response data for significant effects. Included in the exposure-response arrays are LOAELs and NOAELs, based on applied doses. The graphical display allows the reader to quickly compare study outcomes, based on the same or groups of related endpoints for growth and development. In this case, the exposure –response arrays illustrate the concordance and consistency of these effects – meaning that the effects were present in multiple studies and the NOAELs and LOAELs occurred within a narrow dose range.

As illustrated in Figure **3-2**, fetal body weights were decreased with oral (gavage) exposures in several rat studies. Saillenfait (2002) reported fetal body weights decreased by 10% at 250 mg/kg-bw/day and by 47% at the highest dose, 750 mg/kg-bw/day. In the Exxon (1992) study, fetal body weights decreased by 10-11% at 400 mg/kg-bw/day, the highest dose tested. Sitarek et al. (2012) observed 25-30% decrements in pup body weight (PND 4) following maternal exposure to concentrations > 150 mg/kg-bw/day. Because the Sitarek study involved maternal exposures that continued through the postnatal period, the significant decreases in pup body weights observed at PND 4 but not at PND 1 might have been due to toxicity resulting from prenatal exposure to NMP and/or as a result of postnatal transfer of NMP to the pups via lactation.

Figure 3-3 presents the exposure-response array for the inhalation studies in rats. Statistically significant decreases in body weights were observed following inhalation exposure at concentrations ranging from 479 to 612 mg/m^3 in multiple studies (Saillenfait et al., 2003; Hass et al., 1995; Hass et al., 1994; DuPont, 1990). Saillenfait et al. (2003) observed 5-6% decrements in fetal body weights at 486 mg/m^3 and DuPont (1990) observed 7% decrements in fetal body weights at 479 mg/m^3. Two studies by Hass et al. (1995; 1994) also indicated that fetal body weights were decreased in both Wistar and Sprague-Dawley rats; however, both of the Hass studies were excluded by the systematic review process for selection of candidate PODs for this risk evaluation because only one dose level (612 mg/m^3) was used in each study. They are included here because they are used as supporting studies in several previous assessments (U.S. EPA, 2015; RIVM, 2013), and they contribute to the overall weight of evidence. In contrast, no changes in fetal body weight were observed in a study by (Lee et al., 1987).

The DuPont and Hass studies also noted decreased pup body weights (Hass et al., 1995; Hass et al., 1994; DuPont, 1990). In the DuPont study, exposures were suspended from GD 20 through PND 4, but the weight decrement remained, lending support to the notion that decreased body weight is a persistent, adverse effect.

Based on the observations of decreased fetal and postnatal body weights, EPA considered decreased fetal body weights as a potential key endpoint for use in the risk calculation for chronic exposure. These effects were consistent among multiple studies with different dosing regimens and across exposure routes. Reduced fetal body weight is a sensitive endpoint that is considered a marker for fetal growth restriction which is often assumed to be representative of repeated dose rather than acute exposures (van Raaij et al., 2003). Decreases in fetal and postnatal body weights occur at similar dose levels. Decreased fetal body weight was assumed to be the proximate event. In a previous risk evaluation, EPA used this endpoint as the basis for evaluating chronic risks (U.S. EPA, 2015).

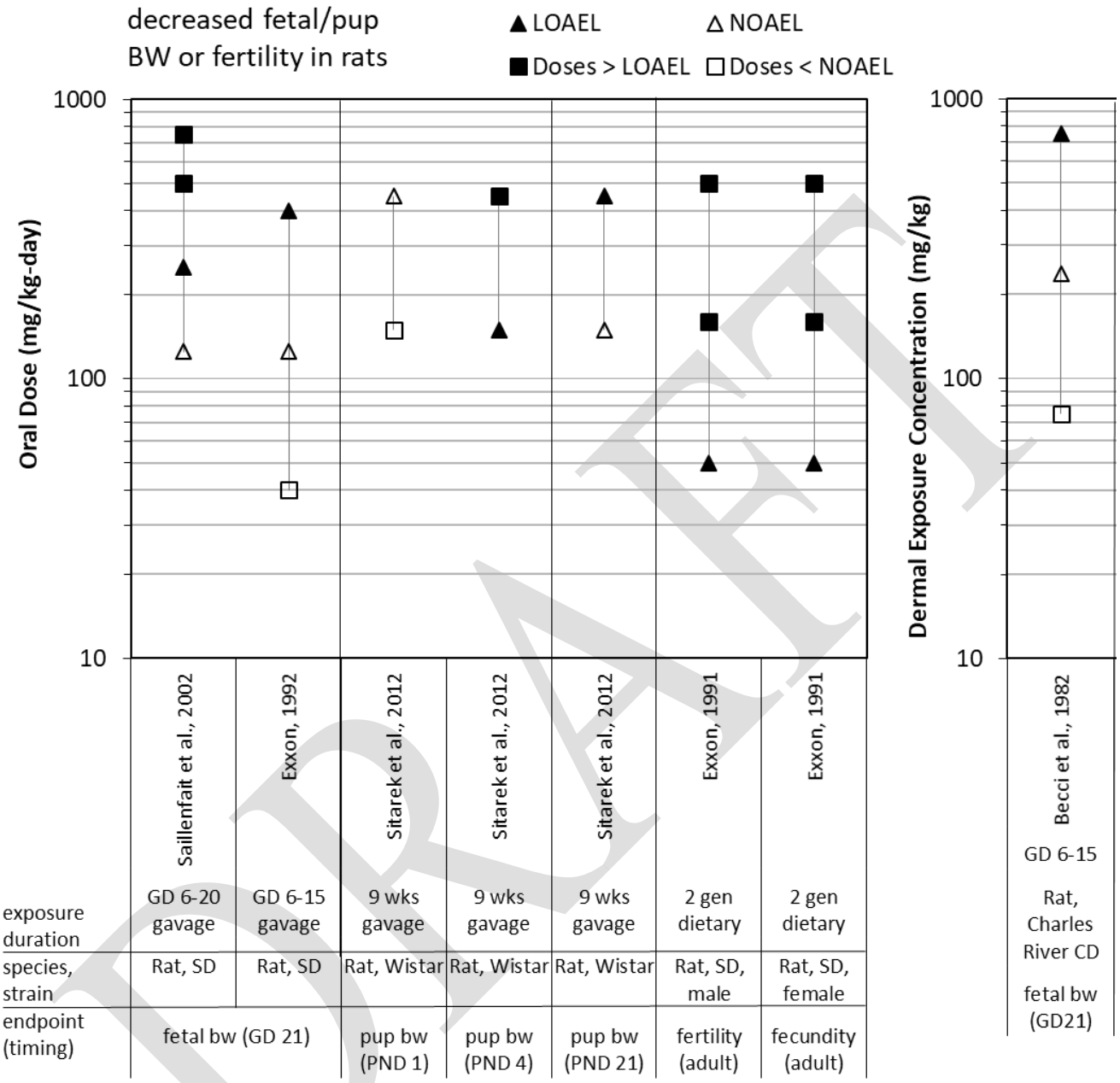


Figure 3-2. Studies that Measured Reproductive and Developmental Effects after Repeated Dose Oral or Dermal Exposure.

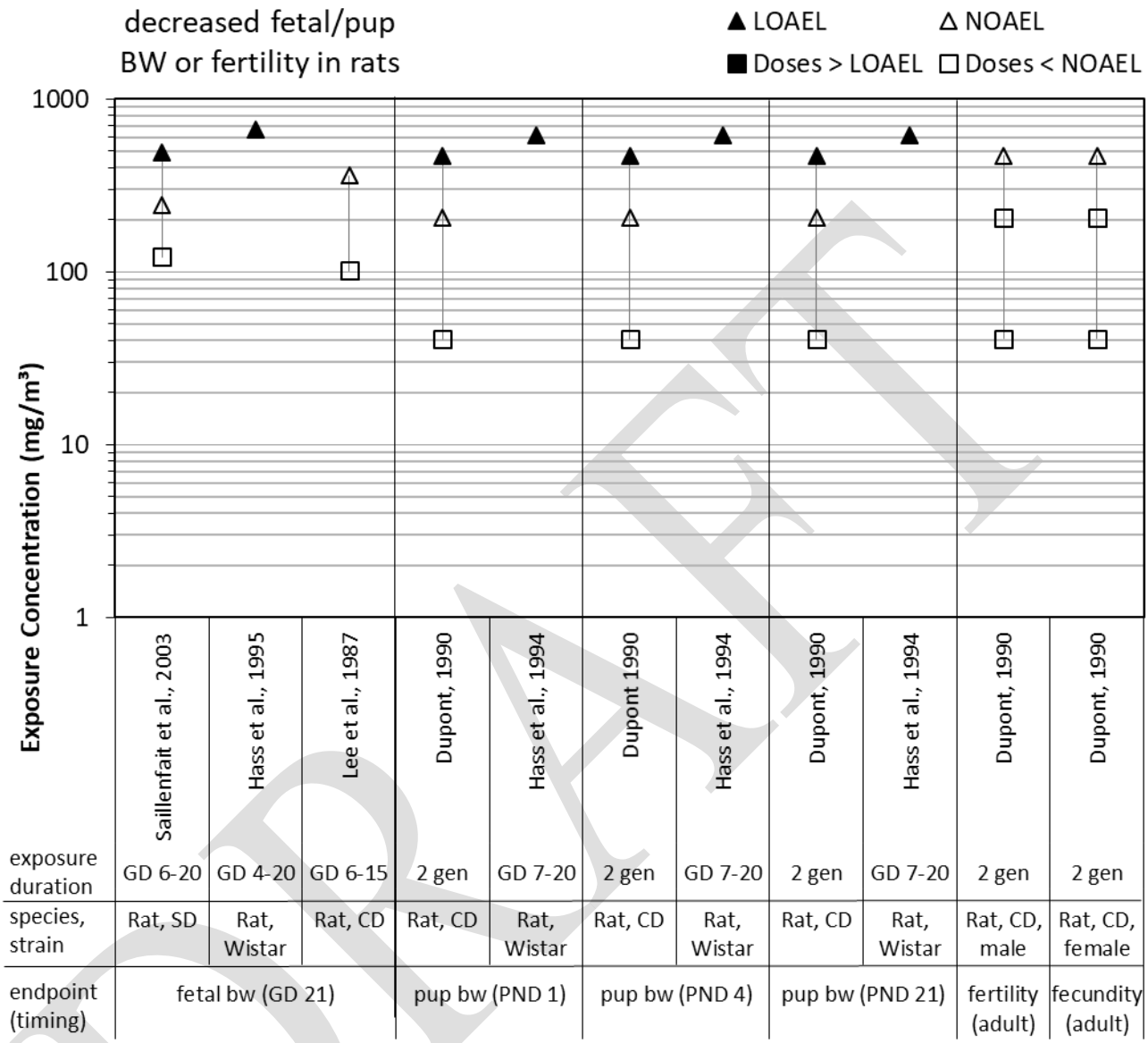


Figure 3-3. Studies that Measured Reproductive and Developmental Effects after Repeated Dose Inhalation Exposure.

Note, the Hass 1994 and Hass 1995 studies were screened out in systematic review because they evaluated effects of a single dose. They were not evaluated for study quality, but they are included here as part of the weight of evidence. The Dupont 1990 study (Solomon et al., 1995; DuPont, 1990) was rated a high-quality study, but it is not consistent with guidelines for 2 generation studies and there were uncertainties about the actual doses achieved at the highest exposure.

Resorptions and Fetal Mortality

Fetal resorptions have been observed in oral, inhalation and dermal studies (Saillenfait et al., 2002; E I Dupont De Nemours & Co, 1990; Becci et al., 1982). Fetal and postnatal mortality have also been observed in oral and dermal studies (Sitarek et al., 2012; NMP Producers Group, 1999a, b; Becci et al., 1982). Statistically significant increases in resorptions or mortality were seen consistently at administered doses of 500 – 1000 mg/kg-bw/day in all studies at the tested doses.

In the single dermal study fetal/pup mortality was increased at 750 mg/kg-bw/day (Becci et al., 1982). In inhalation studies with exposures up to the air saturating concentration, statistically significant increased resorptions or fetal and postnatal pup mortality were not observed, possibly due to the limited NMP exposure concentration. Resorptions and mortality can occur following a single exposure during a sensitive developmental stage and as such, resorptions and fetal and postnatal mortality are considered a relevant endpoint for acute effects (van Raaij et al., 2003).

EPA also considered the relevance of increased postnatal mortality observed in the Sitarek et al. (2012) and NMP Producers Group (NMP Producers Group, 1999a, b) studies. This outcome was not consistently observed in other studies: Sitarek et al. (2012) observed increased pup mortality at 150 mg/kg-bw/day, the NMP producers group studies did not see increased pup mortality until 350 mg/kg-bw/day and no increase in pup mortality was observed in DuPont (1990). When increased post-natal mortality was observed, the NOAELs were within the same range as other sensitive endpoints, such as reduced fetal body weight (e.g., see Table 3-2).

EPA selected increased fetal resorptions/fetal mortality as a key endpoint for the calculation of risks associated with acute exposures. Fetal resorptions (mortality) may result from a single exposure at a developmentally critical period (Davis et al., 2009a; van Raaij et al., 2003; U.S. EPA, 1991b). In the studies reviewed, increased fetal mortality occurred at relatively low exposures, suggesting that this was a sensitive and relevant endpoint, suitable for use in the risk assessment.

Other Fetal Effects

Incomplete ossification was observed following exposures to NMP via oral, inhalation and dermal routes. Incomplete ossification is a decrease in the amount of mineralized bone expected for developmental age and is one of the most common findings in developmental toxicity studies (Carney and Kimmel, 2007). Saillenfait et al. (2002) reported statistically significant increases in incidences of incomplete ossification of sternebrae, skull and thoracic vertebral centra at GD 20 for oral doses of 500 and 750 mg/kg-bw/day. Hass et al. (1995) reported statistically significant increases in delayed ossification of cervical vertebrae 4 through 7 and digital bones following an inhalation exposure at a concentration of 669 mg/m^3. Becci et al. (1982) reported a statistically significant increase in incidences of incomplete ossification of vertebrae at 750 mg/kg-bw/day dermal application. On the other hand, several inhalation exposure studies found no increased incidence of incomplete or delayed ossification (Saillenfait et al., 2003; E I Dupont De Nemours & Co, 1990; Lee et al., 1987).

The areas of increased incomplete ossification that were observed in fetuses at GD 20 or 21 were in bones that are undergoing rapid ossification during the period of observation, but there are a number of hormones considered to be important for regulating skeletal development (Carney and Kimmel, 2007). There are several clues that may be indicative of effects due to something other than generalized delay, including: delays in the presence of specific skeletal malformations, teratogenesis or unusual patterns of delayed ossification (Carney and Kimmel, 2007; van Raaij et al., 2003). Based on the absence of such observations EPA considered NMP-associated delayed ossification to represent a continuum of effects related to delays in fetal growth and development, associated with decreased fetal and/or pup body weight.

Skeletal malformations are considered permanent structural changes that are likely to adversely affect the survival or health of the species (Daston and Seed, 2007) and were observed in some NMP studies

via oral exposure. The Saillenfait et al. (2002) study reported aggregated skeletal malformations (including ribs, vertebrae and others) at GD 20 for oral doses of 500 and 750 mg/kg-bw/day. In contrast, skeletal malformations were not observed in one dermal study and inhalation studies conducted up to the air-saturating concentration. Increased skeletal malformations may not have been observed in the inhalation studies because the vapor pressure of NMP limited the attainment of toxic concentrations in air.

Reduced fertility

Reduced male fertility and female fecundity in the second generation of rats in a two-generation dietary reproductive study (Exxon, 1991) were among the most sensitive reproductive and developmental effects reported in the repeated dose studies reviewed for this risk evaluation (see Figure **3-2**). Evidence of reduced male fertility and female fecundity in this study is further supported by coinciding observations of reduced litter size. It is unknown whether the fertility effects were initiated during gestational, lactational, pubertal, growth, or adult exposures. While other two-generation studies failed to replicate this effect (NMP Producers Group, 1999a, b), reproductive toxicity reported in Exxon (1991) is supported by evidence of effects on fertility following pre-mating exposures in males and female rats described by Sitarek et al. (2012; 2008). Reductions in offspring survival reported following paternal pre-mating exposure (Sitarek and Stetkiewicz, 2008) indicate that reproductive effects may include effects on gametes that impair offspring health and survival. Reduced fertility may therefore be considered part of a continuum of reproductive and developmental effects of NMP exposure.

EPA considered decreased fertility a potential key endpoint for use in the risk calculation for chronic exposures. Reduced male fertility and female fecundity were the most sensitive endpoints reported. Observations from a 2-generation exposure study are supported by effects on male and female fertility following adult exposures. The previous EPA assessment (U.S. EPA, 2015) did not characterize dose-response for these fertility endpoints because the effect observed in the Exxon (1991) study was not replicated in more recent 2-generation studies. However, EPA does not have complete access to the studies that failed to replicate these findings (NMP Producers Group, 1999a, b), and cannot evaluate the validity of the results. Re-evaluation of the Exxon study demonstrates that the study shows a significant effect in the most sensitive reproductive and developmental endpoints identified in the available literature.

Key Endpoints

Developmental effects have consistently been reported following NMP exposure in laboratory animals and a case report provides limited evidence of developmental toxicity in humans. In addition, reproductive effects following NMP exposure have been reported in several animal studies. Collectively the reported effects on reproduction and development, which include reduced male and female fertility, decreased fetal and postnatal body weight, incomplete ossification, skeletal malformations and fetal or postnatal mortality represent a continuum of biologically relevant outcomes that provide important insights for hazard characterization. The developmental effects reported in different studies following NMP exposure occur within a narrow dose range (i.e., 100 to 1000 mg/kg-bw/day for oral and 470 to 669 mg/m^3 for inhalation exposures) and appear to persist based on clinical observations reported through PND 21. EPA considers the general consistency of the NMP treatment effects reported across studies to be supportive of the robustness of the developmental endpoints used for risk evaluation, which exist along a continuum of adverse treatment effects. While reproductive effects are less consistent across studies, reduced fertility is the most sensitive endpoint reported.

EPA has selected fetal resorptions (mortality) as the basis of the dose-response analysis for acute exposures. Acute toxicity studies observing other effects (e.g., LD50 values for acute toxicity or lethality) were not used for the acute POD because the doses at which these effects were observed are higher than those that caused toxic effects in developmental studies. Developmental studies involve multiple exposures (i.e., test substance is administered for 10-15 days); however, they are relevant to single exposures because some developmental effects, such as fetal resorptions and mortality, may result from a single exposure at a developmentally critical period (Davis et al., 2009b; van Raaij et al., 2003; U.S. EPA, 1991b). In an analysis of the utility of developmental toxicity repeat dose studies for use in the assessment of risks following acute exposures, van Raaij et al. compared the potency (NOAELs and LOAELs) of developmental toxicity reported in repeated dose studies and single dose studies (van Raaij et al., 2003). Van Raaij et al. found that there is a relatively small difference between repeated and single dose studies in the NOAELs and LOAELs reported for resorptions and related mortality events and concluded that "resorptions observed in standard guideline based developmental toxicity studies are considered to be relevant endpoints for setting limits for acute exposure." Consequently, EPA determined that these endpoints are most applicable to assessing risks from acute exposures, where the risk of their occurrence is assumed to depend on exceedance of a threshold value for even a single day (i.e., peak concentration) rather than a time weighted average value and the magnitude of the exposure is considered more important for these effects under these study conditions.

EPA selected reduced male fertility, female fecundity and reduced fetal body weights as the basis for the dose-response analysis for chronic exposures. Reduced fertility in male and female rats exposed throughout development and prior to mating in a two-generation reproductive study was the most sensitive reproductive and developmental endpoint identified in the available literature following chronic exposures. Because NMP exposure in this study occurred throughout gestation, post-weaning, growth, and prior to mating, it is unknown whether effects represent a developmental effect or whether they are a result of subsequent exposures. Evidence for sensitive effects on fertility is complemented by robust evidence of developmental toxicity. As documented above, reduced fetal body weight was observed consistently across multiple studies with different dosing regimens and across exposure routes. Reduced fetal body weight is a sensitive endpoint that is considered a marker for fetal growth restriction typically resulting from repeated dosing during gestation rather than a single acute dose (van Raaij et al., 2003). Together, these observations indicate a continuum of reproductive and developmental effects associated with NMP exposure. EPA therefore performed dose-response analysis on all three of these reproductive and developmental endpoints (male fertility, female fecundity, and fetal body weight) for consideration as the chronic POD.

3.2.5.2 Dose Metrics Selected

The selection of the internal dose metric, used to establish "equivalent" exposures, is an important decision in the use of the PBPK model for extrapolation of doses across routes and from rats to humans. Internal dose metric selection is endpoint specific (U.S. EPA, 2006a). For example, the dose metric area-under-the curve (AUC) of the average blood concentration is generally considered appropriate for endpoints associated with repeat dose, assuming that a sustained internal dose of NMP is needed to induce the effects. Endpoints that are associated with a single or short-term acute exposure, assuming that a single dose effect is needed to induce these effects, are generally best evaluated by a metric that captures peak exposure, such as C_{max}.

Reduced fertility following chronic exposure throughout several lifestages is best represented by the AUC of average blood concentration. Similarly, as described above in Section 3.2.4.1, the endpoint of decreased fetal body weight was presumed to be a marker of reduced fetal growth resulting from repeated dose exposure during gestation. Therefore, decreased fetal body weight is expected to be better represented by the AUC of average blood concentration during the vulnerable period of fetal development.

EPA evaluated average AUC (total AUC divided by the number of days, starting from the first day of exposure until the day of measurement), *e.g.*, GD6-20 for Becci et al., (1982) or GD5-21 for Saillenfait et al. (2003) with decreased fetal body weights for oral, inhalation and dermal routes of exposure to confirm the metric is consistent in its estimation of a toxic response across routes. Seven studies that measured fetal body weights were used for evaluating consistency between the internal dose and the response expressed as percent change from control in body weight. The data points were fit to a line and the correlation coefficient (R^2) was used to evaluate linearity, shown in Figure 3-4. The Average Daily AUC metric had a reasonable correlation with fetal body weight changes. Varying the period of averaging for the daily AUC metric may provide higher correlations with fetal body weights.

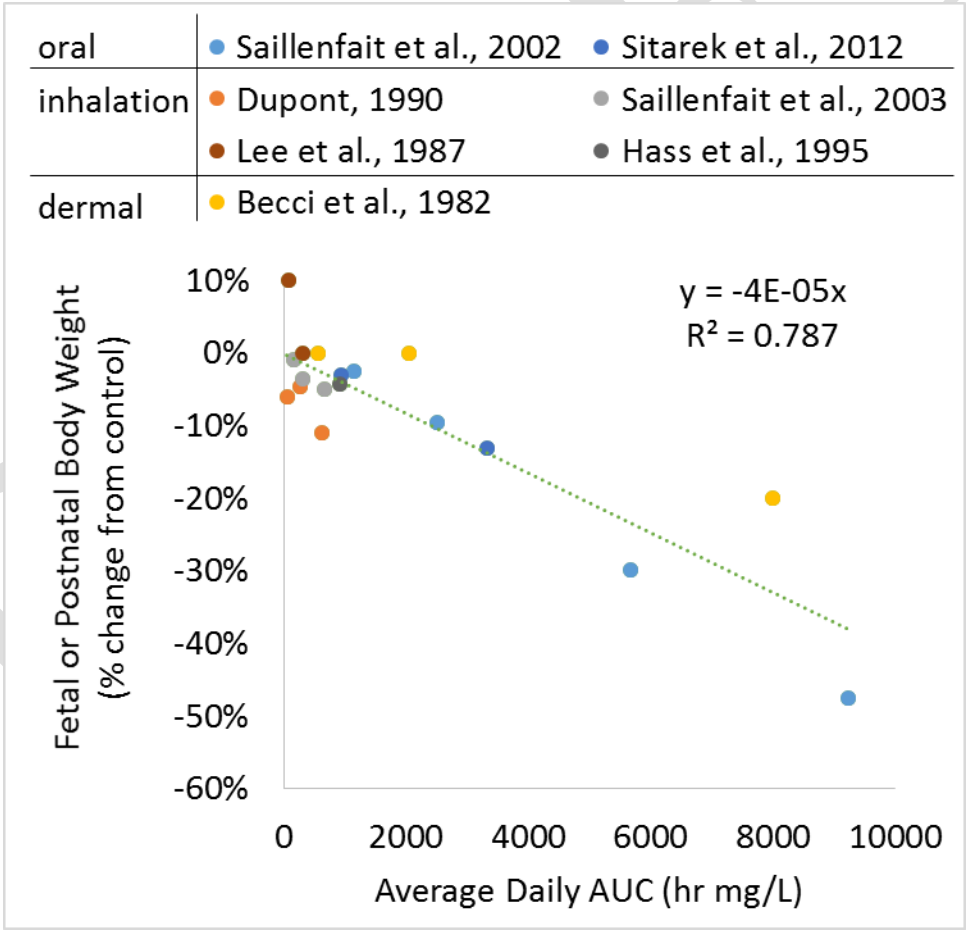


Figure 3-4. Analysis of Fit: Average Daily AUC vs Fetal or Postnatal Body Weight

As described in Section 3.2.5.1, fetal resorptions and fetal mortality are assumed to be associated with acute exposures during fetal development; however, lacking a clear understanding of the possible mode

of action, the best dose metric for the evaluation of fetal resorptions and mortality is unclear. Per EPA guidance (U.S. EPA, 2006a), both AUC and peak blood dose (C_{max}) were used to evaluate this endpoint.

Developmental effects such as fetal mortality and reduced fetal body weight occur following maternal exposure. To identify C_{max} or AUC for developmental effects, BMD modeling was based on internal doses predicted by the PBPK model for adult females. Reproductive effects in the key study were observed following exposure throughout gestation, lactation, puberty, and mating and it is unknown which periods of exposure contributed to reduced fertility. Therefore, internal doses for fertility endpoints were calculated based on internal exposure levels in young post-weaning rats, the life stage at which calculated internal doses are the lowest. EPA performed a sensitivity analysis to determine the effect of this assumption on the POD. BMDLs calculated based on lower internal exposures in young post-weaning rats were up to 2-fold lower than BMDLs calculated based on internal exposures at other life stages.

3.2.5.3 Potentially Exposed and Susceptible Subpopulation

Based on the weight of the scientific evidence, reduced fertility and developmental toxicity are the most sensitive effects of NMP exposure. The lifestages of greatest concern for developmental effects are pregnant women, the developing fetus, and women of childbearing age who may become pregnant. Lifestages of concern for effects on reproductive health and fertility include men and women of reproductive age as well as children and adolescents. The results of one two-generation study in rats (Exxon, 1991) indicate that developmental and early childhood exposure to NMP may contribute to risk of reduced fertility in adulthood. Other potential hazards of NMP identified in Section 3.2.3 may be of concern for other lifestages.

Certain human subpopulations may be more susceptible to exposure to NMP than others. One basis for this concern is that the enzyme CYP2E1 is partially involved in metabolism of NMP in humans and there are large variations in CYP2E1 expression and functionality in humans (Ligocka et al., 2003). The variability in CYP2E1 in pregnant women could affect how much NMP reaches the fetus, which typically does not express CYP2E1 (Hines, 2007). Newborns and very young infants are particularly susceptible to NMP exposure because they are metabolically immature. CYP2E1 is not fully expressed in children until about 90-days of age (Johnsrud et al., 2003). The variability in CYP2E1 was identified as an important uncertainty that was reflected in the calculation of the intraspecies uncertainty factor (human variability). Pre-existing conditions affecting the liver may also impair metabolism of NMP in some individuals. For example, fatty liver disease has been associated with reduced CYP function (Fisher et al., 2009).

Genetic variations or pre-existing conditions that increase susceptibility of the reproductive system, the hepatic, renal, nervous, immune, and other systems targeted by NMP could also make some individuals more susceptible to adverse health outcomes following consumer or workplace exposures. In addition, people simultaneously exposed to other chemicals targeting these systems may also be more susceptible to effects of NMP exposure.

While an uncertainty factor for interindividual variability provides some additional protection for susceptible subpopulations, a lack of quantitative information on the extent to which any of these specific factors increases risk precludes direct incorporation of these factors in the risk characterization.

3.2.5.4 Derivation of Candidate Values

EPA evaluated data from studies described above (Section 3.2.5.1) to characterize NMP's dose-response relationships and select studies to quantify risks for specific exposure scenarios.

In order to select the most appropriate key studies for this analysis, EPA considered the relative merits of the oral, inhalation and dermal animal studies, with respect to: (1) the availability of primary data for statistical analysis; (2) the robustness of the dose-response analysis; and (3) the exposure levels at which adverse effects were observed.

The selected key studies provided the dose-response information for the selection of points of departure (PODs). EPA defines a POD as the dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on the dose for an estimated incidence or a change in response level from a dose-response model (i.e., benchmark dose or BMD), a NOAEL or a lowest-observed-adverse-effect level (LOAEL) for an observed incidence or change in level of response. PODs were adjusted as appropriate to conform to the exposure scenarios derived in Section 2.4.

Studies Selected for BMD Modeling

Studies with only one exposure group (Hass et al., 1995; Hass et al., 1994) were excluded in the systematic review process because they provide limited information about the shape of the dose-response curve and could not be used for BMD modeling. Given their concordance with other studies that had multiple exposure groups they were still seen as supportive of the dose-response relationship. Studies that did not report a statistically significant effect for the endpoint being considered (Lee et al., 1987) may help with dose metric selection, but provide only limited information about the shape of the dose-response curve and were not included in the dose-response assessment of that endpoint.

For reduced fertility EPA selected the following study for dose response analysis:

- Exxon (1991); high quality oral dietary study

For reduced fetal body weights EPA selected the following studies for dose-response analysis:

- Becci (1982); medium quality dermal study
- DuPont (1990); high quality inhalation study
- Saillenfait (2002) high quality oral gavage study
- Saillenfait (2003). high quality inhalation study

For fetal resorptions and increased fetal mortality EPA selected the following studies for dose-response analysis:

- Becci (1982); medium quality dermal study
- Saillenfait (2002); high quality oral gavage study – combined with Saillenfait 2003 based on internal dose.
- Saillenfait (2003) high quality inhalation study
- Sitarek et al. (2012); high quality oral gavage study

The Saillenfait et al. (2002) and Saillenfait et al. (2003) studies administered NMP via different routes but were otherwise similar in study design, using the same exposure duration (GD 6-20) and the same strain of rat (Sprague-Dawley); therefore these studies were combined based on PBPK-derived internal dose metrics to provide additional statistical power for informing the dose-response curve.

EPA guidance recommends a hierarchy of approaches for deriving PODs from data in laboratory animals, with the preferred approach being physiologically-based pharmacokinetic modeling (U.S. EPA, 2012a). When data were amenable, benchmark dose (BMD) modeling was used in conjunction with the PBPK models to estimate PODs. For the studies for which BMD modeling was not possible (Sitarek et al., 2012; Becci et al., 1982), the NOAEL was used for the POD. Details regarding BMD modeling were described in the supplemental file, *Risk Evaluation for N-Methylpyrrolidone (NMP), Benchmark Dose Modeling Supplemental File. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019f). Details regarding the PBPK model can be found in Appendix I.

3.2.5.5 Derivation of Internal Doses

Peer-reviewed PBPK models for NMP in rats and humans (Appendix I) facilitate cross-species extrapolation of hazard information. In this risk evaluation, EPA uses the NMP PBPK models to estimate internal doses (blood concentrations) that may occur in humans and compare these to PODs based on internal doses associated with health hazards in rats. The PBPK models allow EPA to evaluate risks from aggregate exposures by calculating internal doses from combined inhalation and dermal exposures. The models also reduce uncertainty in cross species extrapolation by incorporating toxicokinetic information from rats and humans. To take advantage of these PBPK models, EPA identified PODs in terms of internal doses in rats. Internal doses are expected to have consistent effects regardless of exposure route. EPA therefore used the PBPK model to derive internal dose PODs based on integrated toxicology data from studies using different exposure routes. This section summarizes the toxicokinetics of NMP, the PBPK models and dose metrics used to estimate internal doses in rats.

Toxicokinetic Parameters used in PBPK Modeling

NMP is well absorbed following inhalation, oral and dermal exposures (NMP Producers Group, 1995b). In rats, NMP is distributed throughout the organism and eliminated mainly by hydroxylation to polar compounds, which are excreted via urine. About 80 percent of the administered dose is excreted as NMP and NMP metabolites within 24 hrs. The major metabolite is 5-hydroxy-N-methyl-2-pyrrolidone (5-HNMP). Studies in humans show that NMP is rapidly biotransformed by hydroxylation to 5-HNMP, which is further oxidized to N-methyl- succinimide (MSI); this intermediate is further hydroxylated to 2-hydroxy-N-methylsuccinimide (2-HMSI). The excreted amounts of NMP metabolites in the urine after inhalation or oral intake represented about 100 and 65 percent of the administered doses, respectively (Akesson and Jönsson, 1997).

Dermal absorption of NMP has been extensively studied as it typically poses the greatest potential for human exposure. Dermal penetration through human skin has been shown to be very rapid and the absorption rate is in the range of 1-2 mg/cm^2-hr. These values are 2- to 3-fold lower than those observed in the rat. Prolonged exposures to neat NMP were shown to increase the permeability of the skin. Water reduces the amount of dermal absorption (Payan et al., 2003) while other organic solvents (*e.g.*, d-limonene) can increase it (Huntingdon Life Sciences, 1998). The dermal penetration of 10 percent NMP in water is 100-fold lower than that of neat NMP, while dilution of NMP with d-limonene can increase the absorption of NMP by as much as 10-fold. The dermal absorption of neat NMP under different occlusion conditions indicated that dermal absorption 1 hr post-exposure was greatest under un-occluded conditions (69 percent), followed by semi-occluded (57 percent) and occluded (50 percent) conditions (OECD, 2007b).

Dermal uptake of vapor NMP has been reported in toxicokinetic studies in humans. Bader et al. (2008) exposed volunteers for 8 hrs to 80 mg/m^3 of NMP. Exposure was whole body or dermal-only (*i.e.*, with a respirator). Excretion of NMP and metabolites was used to estimate absorption under different conditions. The authors found that dermal-only exposures resulted in the excretion of 71 mg NMP equivalents whereas whole-body exposures in resting individuals resulted in the excretion of 169 mg NMP equivalents. Under a moderate workload, the excretion increased to 238 mg NMP equivalents. Thus, the authors estimated that the dermal absorption component of exposure from the air will be in the range of 30 to 42 percent under whole-body exposure conditions to vapor.

Previously published PBPK models for NMP in rats and humans were adapted for use by EPA (see Appendix I and U.S. EPA (2015) for details of the PBPK model). The rat version of the model allows for estimation of NMP time-courses in rat blood from inhalation, oral and dermal exposures. The human version of the model, based on non-pregnant and pregnant women, also includes skin compartments for portions of the skin in contact with NMP vapor and liquid and some of those details are described here because it is an important component of human risk.
Analyzing the experimental studies of Akesson et al. (2004), the model yielded an average uptake of 2.1 mg/cm^2-hr of neat NMP, but only 0.24 mg/cm^2-hr of aqueous NMP (1:1 dilution in water). Therefore, distinct values of the liquid permeability constant (PVL), 2.05x10^{-3} cm/h and 4.78x10^{-4} cm/h, were identified from the experimental data. The appropriate value of PVL for neat vs. diluted NMP was used in the respective exposure scenarios in this assessment. Absorption also depends on the partition coefficient (PC) skin:liquid equilibrium, PSKL, which was taken to be the skin:saline PC reported by Poet et al. (2010), PSKL = 0.42 [no units] and assumed not to vary with dilution.

Predicted dermal uptake from liquid exposure is then a function of the liquid concentration, skin surface exposed and duration of contact. The thickness of the liquid film does not factor directly into the estimate. As a conservative estimate for user scenarios it is assumed that fresh material is constantly depositing over the time of use such that the concentration on the skin remains essentially constant at the formulation concentration. This is in contrast to simulations of experimental studies where the volume placed on the skin at the start of the experiment is not replenished (Akesson et al., 2004), in which case the model tracks the amount of NMP remaining in the film and hence the changing concentration for absorption from diluted NMP.

Penetration from vapor was estimated as part of model calibration using the Bader and van Thriel (2006) inhalation data set. This report does not state how the subjects were dressed but the exposures were conducted between late May and mid-June in Germany, so EPA assumed they wore short-sleeved shirts and long pants. While there is no reason to expect that NMP vapors do not penetrate clothing, clothing likely reduces uptake compared to open areas of skin. Since the fitted penetration constant (PV) is multiplied by the skin surface area assumed to be exposed when calculating the penetration rate, these cannot be uniquely determined from the toxicokinetic data. For the purpose of calibration and subsequent modeling, it is assumed that the head, arms and hands are entirely exposed unless personal protection equipment (PPE) is worn. Together the fractional skin area exposed to vapor (SAVC) is 25% of the total skin surface area in the absence of PPE or liquid dermal contact.

The skin:air PC, PSKA, was calculated from the measured skin:saline and blood:saline PCs reported by Poet et al. (2010) and the blood:air PC specified in their model code: PSKA = 44.5. With these values of SAVC and PSKA, the average permeation constant for vapor-skin transport was estimated as PV = 16.4 cm/h. These assumptions and the value of PV resulted in a prediction of 20% of a total uptake from air

(vapor) exposure via the dermal route. In contrast, Bader et al. (2008) measured 42% of total urinary excretion occurring after only dermal exposure to vapors compared to combined inhalation and dermal exposure under resting conditions. The discrepancy between the Bader et al. (2008) data and the current model predictions could be because the subjects in Bader and van Thriel (2006), on which this model is based, wore long-sleeved shirts, thereby reducing dermal absorption or due to the use of an idealized model of inhalation uptake which could over-predict uptake by that route.

For use scenarios in this assessment the air concentration in contact with the skin is assumed to be the same as that available for inhalation with SAVC kept at 25% for consistency, except as specified in the sections below when PPE is worn.

Rat Internal Doses for BMD

EPA used the validated PBPK models for extrapolating NMP doses across routes of exposure and from animals to humans based on NMP-specific data (U.S. EPA, 2015). An internal dose metric such as a measure of toxicant concentration in the blood is expected to be a better predictor of response than the applied dose (*e.g.*, concentration in air) since it is closer to the site of the toxic effect (McLanahan et al., 2012). Further, a good internal dose metric should correlate with or be predictive of toxicity irrespective of the route of exposure by which it occurs. However, this is only true if the metric is in fact a measure of the likelihood of a toxic response or intensity of a toxic effect.

For NMP the existing toxicity data identified the parent (NMP) rather than the metabolites 5-hydroxy-N-methyl-2-pyrrolidone (5-HNMP), N-methylsuccinimide (MSI) or 2-hydroxy-N-methyl-succinimide (2-HMSI) as the proximate toxicant (Saillenfait et al., 2007). Therefore, PBPK model-derived blood concentrations of NMP were considered a better basis than applied dose for the dose-metric used in extrapolation of health effects.

3.2.5.6 Points of Departure for Human Health Hazard Endpoints

PODs for Acute Exposure

Acute exposure was defined for workers as the exposure that occurs over the course of a single day. For consumers, the acute exposure scenario was defined based on completion of a single project on a given day. EPA selected increased resorptions (fetal mortality) as the most relevant endpoint for evaluating risks associated with acute exposure to workers and consumers. Since repeated dose studies were used to investigate this hazard endpoint and the mode of action for NMP is uncertain, EPA assessed dose-response with both the internal dose metrics of C_{max} and AUC.

The Saillenfait et al. (2002); Saillenfait et al. (2003); Becci et al. (1982); and Sitarek et al. (2012) studies were selected for dose-response analysis. The Saillenfait et al. studies measured fetal resorptions and were pooled across exposure routes. The Saillenfait et al. studies also used the same exposure duration (GD 6-20) and the same strain of rat (Sprague-Dawley). Combining the data sets should provide additional statistical power for identifying the BMDL and provide a more robust dose-response (low to high). Moreover, the results for this endpoint were similar, via inhalation and oral exposure routes. Therefore, the combined analysis was retained. A BMR of 1% for increased resorptions/fetal mortality was used to address the relative severity of this endpoint (U.S. EPA, 2012a). Table 3-10 summarizes the calculations leading to the determinations of a POD for each of the studies selected for dose-response analysis.

Table 3-10. Summary of Derivation of the PODs for Fetal Resorptions and Fetal Mortality Following Acute Exposure to NMP

Endpoint and reference (exposure duration/route)	Dose Metric	Model[a]	BMR	BMD Internal dose	BMDL Internal dose	POD	
						Internal dose	Equivalent administered dose (route)[a]
Resorptions							
(Saileenfair et al, 2003; Saillenfait et al., 2002)[d] (GD 6-20, oral and inhalation)	C_{max} (mg/L blood)	Hill	1% RD	429	216	**216**	218 mg/kg bw/day (oral)
	AUC (hr mg/L blood)	Power	1% RD	3343	2128	**2128**	217 mg/kg bw/day (oral)
(Becci et al., 1982) (GD 6-15, dermal)	NOAEL = 237 mg/kg bw/day					662	237 mg/kg bw/day (dermal) 612 mg/kg bw/day (oral)[b]
Fetal Mortality							
(Sitarek et al., 2012) (GD1-PND1, oral)	C_{max} (mg/L)	No model selected[c]	1% RD	N/A	N/A	N/A	264 mg/kg bw/day (oral)
	NOAEL = 450 mg/kg bw/day					265	

RD = relative deviation
Complete documentation of BMD modeling is available in *Risk Evaluation for N-Methylpyrrolidone (NMP), Benchmark Dose Modeling Supplemental File. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019f).
[a] Assuming daily oral gavage and initial BW 0.259 kg (*i.e.* the same experimental conditions as the Saillenfait et al. (2002) study) for the purposes of comparison across the studies.
[b] An oral dose of 612 mg/kg bw/day, given on GD 6-20, is predicted to yield the same peak concentration (662 mg/L).
[c] BMD modeling failed to calculate an adequate BMD or BMDL value by either dose metric and BMD modeling results are presented in the benchmark dose modeling supplemental file.
[d] The combined models for the Saillenfait et al. (2003; 2002) studies do not meet the assumption of homogeneity of variance as recommended for Benchmark Dose Modeling (U.S. EPA, 2012a), however the means are well-modeled; the model with the lowest AIC was selected.

EPA selected the combined analysis of the Saillenfait et al. (2002) oral study and the Saillenfait et al. (2003) inhalation study for the derivation of the POD, 216 mg/L, to be used in the calculation of risk estimates associated with acute exposure. The combination of the two Saillenfait et al. studies provides a larger number of dose levels, hence further characterization of the dose-response curve. Moreover, similar results for this endpoint were obtained in these studies which supports combining them.

Additionally, the Saillenfait et al., studies were amenable to BMD modeling which also accounts for the variability in the observed response. Neither the Becci study nor the Sitarek study were suitable for BMD modeling, hence the NOAEL was used to derive a POD. Accordingly, EPA selected fetal resorptions from the combined Saillenfait et al., studies for use as the basis for calculating risk for acute NMP exposures.

The PODs based on internal dose (AUC and C_{max}) were converted to an equivalent applied dose using the PBPK model. The calculated equivalent administered doses are nearly the same as the NOAELs identified in each study demonstrating consistency between the two methods for deriving PODs.

EPA applied a composite uncertainty factor (UF) of 30 for acute exposure benchmark MOE, based on the following considerations:

- An interspecies uncertainty/variability factor of 3 (UF_A) was applied for animal-to-human extrapolation to account for toxicodynamic differences between species. This uncertainty factor is comprised of two separate areas of uncertainty to account for differences in the toxicokinetics and toxicodynamics of animals and humans. In this assessment, the toxicokinetic uncertainty was accounted for by the PBPK model as outlined in the RfC methodology (U.S. EPA, 1994b). As the toxicokinetic differences are thus accounted for, only the toxicodynamic uncertainties remain, and an UF_A of 3 is retained to account for this uncertainty.
- A default intraspecies uncertainty/variability factor (UF_H) of 10 was applied to account for variation in sensitivity within human populations. The PBPK model did not account for human toxicokinetic variability. Due to limited information on the degree that humans of varying gender, age, health status, or genetic makeup might vary in the disposition of, or response to, NMP a factor of 10 was applied.

PODs for Chronic Exposure

Chronic worker exposure was defined as exposure of 10% or more of a lifetime (U.S. EPA, 2011). Repeated exposures over the course of a work week are anticipated during chronic worker exposure. The most sensitive endpoints were selected based on reproductive and developmental studies on NMP. Adverse developmental outcomes from exposure during critical windows of development during pregnancy can occur any time during the defined chronic worker exposure period. Reproductive toxicity may be of concern for all workers of reproductive age. The in addition to the derivation of the point of departure based on reproductive and developmental toxicity considered repeated exposures, and the POD is expected to be protective of pregnant women and children as well as men and women of childbearing age.

Decreased male fertility, decreased female fecundity and decreased fetal body weight were selected as the endpoints of concern for chronic exposures. The (Exxon, 1991), Becci et al. (1982), (E I Dupont De Nemours & Co, 1990), Saillenfait et al. (2002), and Saillenfait et al. (2003) studies were selected for dose-response analysis. The PBPK model and BMD modeling were applied to these studies to calculate the BMDLs and PODs and BMD modeling results are described in *Risk Evaluation for N-Methylpyrrolidone (NMP), Benchmark Dose Modeling Supplemental File. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019f). A benchmark response (BMR) of 10% for reduced fertility was used. A BMR of 5% relative deviation for decreased fetal body weight was used because in the absence of knowledge as to what level of response to consider adverse, it has been observed that 5% change relative to the control mean is similar to statistically derived NOAELs in developmental studies (Kavlock et al.,

1995). The results are summarized in Table 3-11. It should be noted that the Saillenfait et al., studies were analyzed both separately and combined. Also, the PBPK model was used to present the POD as the equivalent applied oral dose, to allow for comparison.

Table 3-11. Summary of Derivation of the PODs for Reproductive and Developmental Effects Following Chronic Exposure to NMP

Endpoint and reference (exposure duration/route)	Model[a]	BMR	BMD Internal dose AUC (hr mg/L blood)	BMDL Internal dose AUC (hr mg/L blood)	POD	
					Internal dose AUC (hr mg/L blood)	Equivalent applied oral dose[a]
Fetal Body Weight						
(Saillenfait et al, 2003; Saillenfait et al., 2002) (GD 6-20, oral and inhalation)	Exponential (M5)[b]	5% RD	1937	1424	1424	152 mg/kg bw/day
(Saillenfait et al., 2002) (GD 6-20 oral)	Exponential (M5)	5% RD	1637	1184	1184	129 mg/kg bw/day
(Saillenfait et al., 2003) (GD 6-20 inhalation)	Linear	5% RD	652	411	411	48 mg/kg bw/day
(E I Dupont De Nemours & Co, 1990) (preconception exposure, GD 1–20, inhalation)	Exponential (M2)	5% RD	315	223	223	27 mg/kg bw/day
(Becci et al., 1982) (GD 6-15, dermal)	Polynomial (3°)	5% RD	5341	4018	4018	375 mg/kg bw/day
Reduced Male Fertility						
(Exxon, 1991) (Dietary exposure throughout gestation, lactation, growth, pre-mating)	Log-logistic	10% ER	492[c1] 341[c2]	262[c1] 183[c2]	**183**	28 mg/kg bw/day
Reduced Female Fecundity						
(Exxon, 1991) (Dietary exposure throughout gestation, lactation, growth, pre-mating)	Log-logistic	10% ER	862[c1] 420[c2]	401[c1] 202[c2]	202	31 mg/kg bw/day

Endpoint and reference (exposure duration/route)	Model[a]	BMR	BMD Internal dose AUC (hr mg/L blood)	BMDL Internal dose AUC (hr mg/L blood)	POD	
					Internal dose AUC (hr mg/L blood)	Equivalent applied oral dose[a]
RD = relative deviation; ER= extra risk The POD selected for calculating risk of chronic NMP exposures is highlighted in bold. Complete documentation of BMD modeling is available in *Risk Evaluation for N-Methylpyrrolidone (NMP), Benchmark Dose Modeling Supplemental File. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019f). [a] Assuming daily oral gavage GDs 6-20 and initial BW 0.259 kg (*i.e.* the same experimental conditions as the Saillenfait et al. (2002) study) for the purposes of comparison across the studies. [b] The Saillenfait et al. (2003; 2002) studies do not meet the assumption of homogeneity of variance as recommended for Benchmark Dose Modeling (U.S. EPA, 2012a), however the means are well-modeled. EPA evaluated the impact on the BMDL of the smallest observed standard deviation for all dose levels, the largest standard deviation and the pooled standard deviation. The BMDLs differed by less than 25% which provides assurance that the impact of the variances on the BMDL was minimal. [c] In the Exxon (1991) study, each dam had two sets of mating periods. Each mating period was analyzed separately. C1 indicates results for the first mating period and C2 indicates results from the second mating period. PODs for male fertility and female fecundity in this study are calculated based on exposure levels in 50g rats immediately post-weaning.						

EPA selected the POD derived from decreased male fertility (183 hr mg/L) in a two-generation reproductive study (Exxon, 1991) to be used in the calculation of risk estimates associated with chronic exposures. This high-quality study identified the most sensitive reproductive endpoints and had a significant dose-response relationship that was adequately modeled by the BMD model. The POD for effects on reduced female fecundity in this study was very similar (202 hr mg/L) to the POD for effects on male fertility, making it highly relevant to both male and female reproductive endpoints. This POD is consistent with EPA's Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996)

The selected chronic POD is also protective of developmental toxicity endpoints of concern for pregnant women, including reduced fetal body weight. The PODs derived from effects on fetal body weight in two developmental inhalation exposure studies Saillenfait et al. (2003); (E I Dupont De Nemours & Co, 1990) fall in an internal dose range (411 and 223 hr mg/L), similar to the POD based on reduced fertility, lending further support for the selected POD. Both inhalation studies used whole body exposures where dermal absorption of NMP vapors likely contributed to the toxicity. This is similar to human exposure scenarios; however, the unknown differences between human and rat dermal absorption of NMP vapor adds uncertainty to values derived from either of these studies alone. While the POD for the DuPont study was lower than the Saillenfait study, the dose-response relationship in the DuPont study was not as robust as the Saillenfait study. Lower variability in body weights was observed in the Saillenfait study than in the DuPont study, where statistically significant differences only occurred in the lowest and highest dose groups, not the middle dose group.

The combination of the Saillenfait et al. (2002) and Saillenfait et al. (2003) studies provided a more extensive characterization of the dose-response curve across exposure routes. However, the Saillenfait et al. (2003) study observed a statistically significant decrease in fetal body weights at an internal dose that corresponds to an oral dose lower than the NOAEL in the Saillenfait et al. (2002) oral study. This implies that fetal body weights were more sensitive to inhalation exposures and this was not fully accounted for in the PBPK model. Therefore, the combined analysis was not retained.

There are limitations to the Becci study: the duration of dosing was shorter than for the Saillenfait studies and it resulted in a higher POD. The uncertainty regarding exposure duration and sampling time leads to uncertainty about recovery and compensation. Therefore, this study was not selected for the POD.

The PODs based on internal dose (AUC) were converted to an equivalent applied dose using the PBPK model. The calculated equivalent administered doses are nearly the same as the NOAELs identified in each study (where available) demonstrating consistency between the two methods for deriving PODs.

EPA applied a composite uncertainty factor (UF) of 30 for chronic exposure benchmark MOE, based on the following considerations:

- An interspecies uncertainty/variability factor of 3 (UF_A) was applied for animal-to-human extrapolation to account for toxicodynamic differences between species. This uncertainty factor is comprised of two separate areas of uncertainty to account for differences in the toxicokinetics and toxicodynamics of animals and humans. In this assessment, the toxicokinetic uncertainty was accounted for by the PBPK model as outlined in the RfC methodology (U.S. EPA, 1994b). As the toxicokinetic differences are thus accounted for, only the toxicodynamic uncertainties remain, and an UF_A of 3 is retained to account for this uncertainty.
- A default intraspecies uncertainty/variability factor (UF_H) of 10 was applied to account for variation in sensitivity within human populations. The PBPK model did not account for human toxicokinetic variability. Due to limited information on the degree of humans of varying gender, age, health status, or genetic makeup might vary in the disposition of, or response to, NMP a factor of 10 was applied.

3.2.6 Summary of Human Health Hazards

Table 3-12 summarizes the hazard studies, health endpoints and UFs that are considered relevant for this risk evaluation. The reported PODs reflect internal dose estimates (blood concentrations) for comparison with internal dose estimates of human exposures from multiple routes (e.g., inhalation and/or dermal).

Table 3-12. PODs Selected for Non-Cancer Effects from NMP Exposures

Exposure Duration	Target System	Species	Dose Metric	BMR	POD	Effect	Uncertainty Factors (UFs) for Benchmark MOE	References	Data Quality Score
Acute	Developmental	Rat	Cmax (mg/L)	1% RD	216	Fetal Resorptions and Fetal Mortality	UF_A = 3 UF_H = 10 Total UF = 30	(2003; Saillenfait et al., 2002)	High
Chronic	Reproductive	Rat	AUC (hr-mg/L)	10% ER	183	Decreased Male Fertility	UF_A = 3 UF_H = 10 Total UF = 30	(Exxon, 1991)	High
RD = relative deviation; ER= extra risk; UF_A = interspecies UF; UF_H = intraspecies UF (U.S. EPA, 2002).									

Primary Strengths

There is a robust dataset for the critical reproductive and developmental effects that serve as the basis for the PODs used in this risk characterization. The available studies demonstrate clear, consistent effects on a continuum of reproductive and developmental endpoints following NMP exposure across oral, inhalation, and dermal exposure routes. Each of the critical endpoints supporting the PODs represents an adverse effect that is biologically relevant to humans. The acute POD based on fetal mortality reflects consistent observations across multiple high-quality studies using multiple exposure routes. The chronic POD selected based on reduced fertility following exposure across lifestages in a high-quality study is supported by other high-quality studies demonstrating reduced fertility in males and females exposed only as adults. The POD derived from reduced fertility is within close range of PODs derived from a developmental endpoint (fetal body weight) that is consistently observed across studies, species, and routes of exposure. The quality of the studies, consistency of effects, relevance of effects for human health, coherence of the spectrum of reproductive and developmental effects observed and biological plausibility of the observed effects of NMP contribute to the overall confidence in the PODs identified based on reproductive and developmental endpoints.

The NMP PBPK models allow EPA to identify points of departure based on blood concentrations of NMP that are associated with effects in animal models. Because the effects of NMP at a specific blood concentration are independent of exposure route, a single internal dose POD can be applied to evaluate risk from all routes of exposure. This eliminates the need for extrapolating hazard information across exposure routes. The PBPK model also accounts for toxicokinetic information in rats and humans, reducing a source of uncertainty associated with cross-species extrapolation.

Primary Limitations

While there is a large amount of animal data on reproductive and developmental effects of NMP, there are not studies on reproductive and developmental toxicity of NMP in humans. Therefore, this risk evaluation relies on the assumption that reproductive and developmental toxicity observed in animal models is relevant to human health. It is unknown whether this assumption leads to an underestimate or overestimate of risk.

Some potentially sensitive endpoints remain poorly characterized. For example, neurodevelopmental effects were observed in response to a high dose exposure, but no NOAEL has been established for these effects. If endpoints that are not well characterized are in fact more sensitive to NMP than the endpoints that serve as the basis for the POD, this could lead to an underestimation of risk.

There are some uncertainties associated with the specific endpoint used as the basis for the chronic POD. There are a limited set of studies available to EPA on the specific endpoint used as the basis for the POD. The chronic POD is based on sensitive reproductive endpoints observed in a 2-generation reproductive study. Two of the subsequent studies that evaluated fertility in 2-generation reproductive studies were not fully available to EPA for review. A third 2-generation study via inhalation exposure was available but deviated substantially from EPA and OECD guidelines and had serious limitations due to uncertainties about the actual doses achieved, making it difficult to draw clear conclusions from the results. Although the critical effect is only observed in a single study, it is supported by evidence in other high-quality studies of reduced fertility in male and female rats exposed as adults. It is unclear whether this data limitation leads to an overestimate or underestimate of risk.

In addition, because exposure in the key study occurred throughout gestation, lactation, post-weaning, puberty and pre-mating, it is not possible to determine which exposure periods contributed to reduced fertility. EPA therefore established a POD based on lifestage at which the lowest level of exposure relative to body weight occurred. This assumption could contribute to an overestimate of risk.

There is some uncertainty around the techniques used to generate NMP air concentrations for animal exposures in some supporting studies considered in the weight of evidence. Experimental conditions may have inadvertently resulted in the inclusion of aerosolized particles in the exposure chamber in some inhalation exposure studies. NMP is hygroscopic; therefore, variations in temperature, humidity and/or test protocol (e.g., the number of air changes, use of a spray or nebulization technique to generate test atmospheres) may impact the NMP air saturation concentration, resulting in condensation of NMP. Aerosol formation would result in increased dermal and/or oral exposures (from grooming behavior) in addition to the intended inhalation exposure. For example, the 2-generation inhalation study (Solomon et al., 1995; E I Dupont De Nemours & Co, 1990) noted that condensation observed on the chamber walls at the highest dose indicates that the actual air concentrations of NMP were lower than the intended exposure. Nonetheless, higher test concentrations and total body exposures to NMP were associated with adverse developmental effects in rats.

Overall Confidence

EPA has high confidence in the acute and chronic PODs identified for evaluating risk from NMP. The PODs are derived from endpoints that fall along a continuum of reproductive and developmental effects that are consistently observed in response to NMP across oral, dermal and inhalation exposure routes. Application of the PBPK model reduces uncertainties associated with extrapolation across species and exposure routes, further contributing to overall confidence in the PODs.

4 RISK CHARACTERIZATION

4.1 Environmental Risk

4.1.1 Risk Estimation Approach

The environmental risk of NMP is characterized by calculating risk quotients or RQs (U.S. EPA, 1998; Barnthouse et al., 1982). The RQ is defined as:

RQ = Environmental Concentration / Effect Level

An RQ equal to 1 indicates that the exposures are the same as the concentration that causes effects. If the RQ is above 1, the exposure is greater than the effect concentration. If the RQ is below 1, the exposure is less than the effect concentration. The Effect Levels or Concentrations of Concern (COCs) used to calculated RQs are identified in Section 3.1.2 and are shown in Table 4-1.

Table 4-1. Concentrations of Concern (COCs) for Environmental Toxicity

Environmental Toxicity	Most Sensitive Species	Concentration of Concern (COC)
Acute Toxicity, aquatic organisms	48-Hour aquatic invertebrates	100,000 µg/L
Chronic Toxicity, aquatic organisms	21-Day aquatic invertebrates	1,770 µg/L

EPA used estimated acute and chronic exposure concentrations of NMP in surface water (Section 2.3.2) and acute and chronic concentrations of concern (COCs) (Section 3.1.2) to evaluate the risk of NMP to aquatic species using Table 4-2 summarizes the risk quotients (RQs) for the acute and chronic risk of NMP. The RQ values for acute and chronic risks are 0.0022 and 0.85, respectively. Based on these values risks are not indicated for either acute or chronic exposure pathways. As previously stated, an RQ below 1 indicates that the exposure concentrations of NMP is less than the concentrations that would cause an effect to organisms in the aquatic exposure pathways.

Table 4-2. Calculated Risk Quotients (RQs) for NMP

	Maximum Exposure Concentration	Concentrations of Concern (COC)	RQ
Acute Risk Scenario	224 µg/L	100,000 µg/L	0.0022
Chronic Risk Scenario	1,496 µg/L	1,770 µg/L	0.85

Based on the calculated RQs for acute and chronic risk scenarios, EPA concludes that NMP demonstrates a low hazard to environmental receptors. Based on the RQ values, EPA also concludes that NMP does not present unreasonable risks to the environment.

4.1.2 Assumptions and Key Uncertainties for the Environment

In the NMP Problem Formulation (U.S. EPA, 2018c) and this RE, EPA completed a screening level evaluation of environmental risk using inherently conservative assumptions. The analysis was completed using "high-end" estimated concentrations of NMP in the aquatic environment as described in Section 2.3.2 and compared those acute and chronic exposure estimates to conservative measures of acute and chronic hazard (concentrations of concern) as described in Section 3.1.2. EPA in the NMP Problem Formulation (U.S. EPA, 2018c) did not conduct any further analyses on pathways of exposure for terrestrial receptors as described in Section 2.5.3.1 of the NMP Problem Formulation and further described in Section 2.2 and 2.3 of this RE.

4.2 Human Health Risk

The human health risks associated with NMP conditions of use identified in Section 1.4 are discussed below. Specific information regarding the methodologies used to derive exposure estimates, including related assumptions and data limitations or uncertainties can be found in Section 2.4; an overview of the potential human health hazards, including key and supporting studies is presented in Section 3.2.

4.2.1 Risk Estimation Approach

Acute or chronic MOEs were used in this assessment to estimate non-cancer risks using Equation 4-1. EPA calculated MOEs and compared them to the benchmark MOE to interpret the MOE risk estimates for each exposure scenario. The MOE estimate was interpreted to have negligible human health risk if the MOE estimate was greater than the benchmark MOE (i.e., the total UF). Typically, the larger the MOE, the more unlikely it is that a non-cancer adverse effect would occur.

Equation 4-1. Equation to Calculate Non-Cancer Risks Following Acute or Chronic Exposures Using Margin of Exposures

$$MOE = \frac{Non-cancer\ Hazard\ value\ (POD)}{Human\ Exposure}$$

Where:

MOE = Margin of exposure (unitless)
(POD) = internal dose (Cmax, mg/L or AUC hr mg/L)
Human Exposure = internal dose exposure estimate (Cmax, mg/L or AUC hr mg/L) from occupational or consumer exposure assessment. Cmax was used for acute exposure scenarios and the AUC was used for chronic exposure scenarios.

In this risk characterization, peer-reviewed PBPK models for NMP in rats and humans (Appendix I) allow EPA to estimate internal doses (blood concentrations) that may occur in humans and compare these to PODs based on internal doses associated with health hazards in rats. MOEs are calculated by dividing PODs in units of internal blood concentrations in rats by human blood concentrations expected for specific exposure scenarios. For characterization of acute risks, PODs and human exposure estimates are in terms of maximum blood concentrations (Cmax) while for chronic risks, they are in terms of total daily exposure (AUC).

The PBPK models facilitate integration of exposure and hazard information across exposure routes. For each exposure scenario, the PBPK model is used to aggregate simultaneous inhalation and dermal exposures into a single human internal dose. The relative contribution of inhalation and dermal exposure routes varies across exposure scenario. The PBPK models also allow the risk characterization to incorporate information about toxicokinetics. Internal doses predicted by the model account for internal exposure that remains after external exposure has ceased, reflecting the rate of metabolism and elimination. Toxicokinetic information captured in rat and human models reduces toxicokinetic uncertainty associated with interspecies extrapolation.

Table 4-3 and Table 4-4 summarize the use scenarios, populations of interest and toxicological endpoints used to evaluate risk for acute and chronic exposures for workers and acute exposure for consumers, respectively.

Table 4-3. Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Occupational Risks Following Acute and Chronic Exposures to NMP

Populations and Toxicological Approach	Occupational Use Scenarios of NMP	
Population of Interest and Exposure Scenario:	***Users:*** Adults and youth of both sexes (>16 years old) exposed to NMP during product use in a workday, typically 8 or 12 hours.[1, 2] ***Occupational Non-users:*** Adults and youth of both sexes (>16 years old) indirectly exposed to NMP while in the vicinity of product use.	
Health Effects of Concern, Concentration and Time Duration	***Acute Non-Cancer Health Effects:*** Developmental toxicity (fetal mortality). ***Hazard Values (POD):*** 216 mg/L (Cmax)	***Chronic Non-Cancer Health Effects:*** Reproductive toxicity (reduced fertility) ***Hazard Values (POD):*** 183 hr-mg/L (AUC)
Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations	UFs for Acute Hazard: Total UF = 30 (10X UF_H * 3X UH_A)[3]	UFs for Chronic Hazard: Total UF = 30 (10X UFH * 3X UHA)[3]

Notes:

[1] It is assumed that there is no substantial buildup of NMP in the body between exposure events due to NMP's short biological half-life (~2.5 hrs).

[2] EPA expects that the users of NMP-based products and exposed non-users are generally adults, but younger individuals may be users and exposed non-users.

[5] UF_H=intraspecies UF; UF_A= interspecies UF

Table 4-4. Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Consumer Risks Following Acute Exposures to NMP

Populations and Toxicological Approach	Consumer Use Scenarios of NMP
Population of Interest and Exposure Scenario:	***Users:*** Adults of both sexes (>16 years old) typically exposed to NMP[1, 2] ***Bystanders:*** Individuals of any age indirectly exposed to NMP while being in the rest of the house during product use see Section 2.4.2 for more information.
Health Effects of Concern, Concentration and Time Duration	***Non-Cancer Health Effects:*** Developmental toxicity (fetal mortality). ***Hazard Values (POD):*** 216 mg/L (Cmax)
Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations	Total UF = 30 (10X UF_H * 3X UH_L)[3]

[1] It is assumed that there is no substantial buildup of NMP in the body between exposure events due to NMP's short biological half-life (~2.5 hrs).
[2] EPA expects that the users of these products are generally adults, but younger individuals may be users of NMP-based paint strippers.
[3] UFH=intraspecies UF; UFA= interspecies UF

4.2.2 Risk Estimation for Exposures for Occupational Use of NMP

The risk characterization was performed using internal dose estimates derived from PBPK modeling of occupational exposures based on available monitoring data. The following sections present the results of the PBPK modeling results for risk estimation of acute and chronic inhalation and dermal exposures following occupational use of NMP in each condition of use. MOE values that are bold are below the benchmark MOE of 30 (described in Section 3.2.5.6).

For each occupational exposure scenario, EPA predicted the likelihood of glove use based on the characteristics described in Table 2-3. For scenarios that have only industrial sites, EPA assumes that SDS recommendations are followed and that workers are likely to wear protective gloves and have specialized training on the proper usage of these gloves, corresponding to a protection factor of 20. In scenarios that cover a variety of commercial and industrial sites, EPA assumes that either no gloves are used or if gloves are used, that occlusion may occur for some high-end exposure scenarios, corresponding to a protection factor of 1. If occlusion were to occur, contact duration would be extended. Based on the widespread use of NMP in these occupational scenarios, EPA assesses a central tendency scenario assuming the use of gloves with minimal to no employee training, corresponding to a protection factor of 5. For the Recycling and Disposal scenarios, EPA assesses both high-end and central tendency scenarios assuming the use of gloves with basic employee training, corresponding to a

protection factor of 10. As indicated in Table 2-3, use of protection factors above 1 is valid only for glove materials that have been tested for permeation against the NMP-containing liquids associated with the condition of use.

For high-end scenarios where glove use without occlusion was assumed and MOEs were above the benchmark MOE, EPA conducted additional modeling of exposures for no glove use to determine whether lack of glove use could result in MOEs below the benchmark MOE. For high-end scenarios where no glove use was assumed and MOEs were below the benchmark MOE, EPA conducted additional modeling of exposures for glove use to determine whether glove use could result in MOEs above the benchmark MOE.

More information on glove materials for protection against NMP is in Appendix E.

4.2.2.1 Manufacturing of NMP

Table 4-5. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Use of NMP in Manufacturing [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 10	Gloves PF 20	No gloves	Gloves PF 10	Gloves PF 20	
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	4.2	0.42	0.21	52	518	1025	30
		High-End	21.9	2.14	1.11	**9.9**	101	194	

[a] MOEs < 30 are indicated in bold
[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction (EPA expects 100% NMP for this condition of use). High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction (EPA expects workers use 100% NMP for this condition of use).

MOEs calculated using central tendency estimates for acute exposure to workers during bulk container unloading are above the benchmark MOE (30) in the absence of glove use. One MOE calculated using a high-end estimate for acute exposure to workers during drum unloading is below the benchmark MOE in the absence of glove use; the MOE calculated using a glove protection factor (PF 10) is above the benchmark MOE.

Table 4-6. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Use of NMP in Manufacturing [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b]	Chronic Exposure, AUC (hr mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 10	Gloves PF 20	No gloves	Gloves PF 10	Gloves PF 20	
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	8.6	0.86	0.43	**21**	213	423	30
		High-End	81.4	7.4	3.82	**2.2**	**25**	48	

[a] MOEs < 30 are indicated in bold
[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction (EPA expects 100% NMP for this condition of use). High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction (EPA expects 100% NMP for this condition of use).

MOEs calculated for manufacturing using central tendency and high-end estimates of chronic exposure to workers are below the benchmark MOE (30) in the absence of glove use and above the benchmark

MOE with the incorporation of glove protection factors (PF 10 and PF 20 for central tendency and high-end estimates, respectively).

EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence.

Primary Strengths

EPA assessed dermal exposure to liquids using the most recent CDR data for concentration provided by industry submitters. Modeling, in the middle of the approach hierarchy, was used to estimate occupational air concentrations for both the loading of NMP into bulk containers and into drums. For modeling of these air concentrations, EPA attempted to address variability in input parameters by estimating both central tendency and high-end parameter values. Additionally, for modeling of air concentrations during the loading of drums, EPA used Monte Carlo simulation to capture variability in input parameters. EPA expects the duration of inhalation and dermal exposure to be realistic for loading activities, as these durations are based on the length of time required to load NMP into specific container sizes (i.e., tank trucks, rail cars, and drums).

Primary Limitations

The representativeness of the estimates of duration of inhalation and dermal exposure for the loading activities toward the true distribution of durations for all worker activities in this occupational exposure scenario is uncertain. NMP concentration is reported to CDR as a range and EPA assessed only the upper end of the range since a central value cannot be ascertained for this scenario. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage is likely based on judgment. The assumed glove protection factor values are highly uncertain. EPA is uncertain of the accuracy of emission factors used to estimate fugitive NMP emissions and thereby model NMP air concentrations. The representativeness of the modeling results toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium. The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.2.2 Repackaging

Table 4-7. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Use of NMP in Importation and Repackaging [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 10	Gloves PF 20	No gloves	Gloves PF 10	Gloves PF 20	
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	4.2	0.42	0.21	52	518	1025	30
		High-End	21.9	2.14	1.11	**9.9**	101	194	

[a] MOEs < 30 are indicated in bold
[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction (EPA expects 100% NMP for this condition of use). High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction (EPA expects 100% NMP for this condition of use).

MOEs calculated for importation and repackaging using central tendency estimates of acute exposure to NMP are above the benchmark MOE (30) in the absence of glove use. One MOE calculated using a high-end estimate for acute exposure (without gloves) is below the benchmark MOE; the MOE calculation incorporating a glove protection factor (PF 10) is above the benchmark MOE.

Table 4-8. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Use of NMP in Importation and Repackaging [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b]	Chronic Exposure, AUC (hr mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 10	Gloves PF 20	No gloves	Gloves PF 10	Gloves PF 20	
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	8.6	0.86	0.43	**21**	213	423	30
		High-End	81.4	7.4	3.82	**2.2**	**25**	48	

[a] MOEs < 30 are indicated in bold
[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction (EPA expects 100% NMP for this condition of use). High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction (EPA expects 100% NMP for this condition of use).

MOEs calculated for importation and repackaging using central tendency and high-end estimates of chronic exposure to workers are below the benchmark MOE (30) in the absence of glove use; central tendency estimates are above the benchmark MOE with gloves (PF 10). One MOE calculated using a high-end estimate for chronic exposure to workers with gloves (PF 10) is below the benchmark MOE.

Although the MOE calculation incorporating a glove protection factor (PF 20) is above the benchmark MOE, EPA has not found information that would indicate specific activity training (e.g., procedure for glove removal and disposal) for tasks where dermal exposure can be expected to occur in industrial OES. The PF 20 glove protection factor is not assumed for any central tendency or high-end exposure estimates.

EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence.

Primary Strengths

EPA assessed dermal exposure to liquids using the most recent CDR data for concentration provided by industry submitters. Modeling, in the middle of the approach hierarchy, was used to estimate occupational inhalation exposure concentrations for both the unloading of NMP from bulk containers and from drums. For modeling of these air concentrations, EPA attempted to address variability in input parameters by estimating both central tendency and high-end parameter values. Additionally, for modeling of air concentrations during the loading of drums, EPA used Monte Carlo simulation to capture variability in input parameters. EPA expects the duration of inhalation and dermal exposure to be realistic, as the durations are based on the length of time to load NMP into specific container sizes (i.e., tank trucks, rail cars, and drums).

Primary Limitations

The representativeness of the estimates of duration of inhalation and dermal exposure for the unloading activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. NMP concentration is reported to CDR as a range and EPA assessed only the upper end of the range since a central value cannot be ascertained for this scenario. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage is likely based on judgment. The assumed glove protection factor values are highly uncertain. EPA is uncertain of the accuracy of the emission factors used to estimate fugitive NMP emissions and thereby to model NMP air concentrations. The representativeness of the modeling results toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium. The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.2.3 Chemical Processing, Excluding Formulation

Table 4-9. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Use of NMP in Chemical Processing (Excluding Formulation) [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 10	Gloves PF 20	No gloves	Gloves PF 10	Gloves PF 20	
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	3.5	0.35	0.18	62	612	1198	30
		High-End	7.0	0.72	0.37	30.8	301	579	

[a] MOEs < 30 are indicated in bold
[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction (EPA expects 100% NMP for this condition of use). High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction (EPA expects 100% NMP for this condition of use).

MOEs calculated for chemical processing (excluding formulation) using central tendency and high-end estimates of acute exposure to NMP are above the benchmark MOE (30) in the absence of glove use.

Table 4-10. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Use of NMP in Chemical Processing (Excluding Formulation) [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b]	Chronic Exposure, AUC (hr mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 10	Gloves PF 20	No gloves	Gloves PF 10	Gloves PF 20	
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	6.2	0.63	0.32	**29**	291	570	30
		High-End	12.7	1.3	0.67	**14**	143	275	

[a] MOEs < 30 are indicated in bold
[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction (EPA expects 100% NMP for this condition of use). High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction (EPA expects 100% NMP for this condition of use).

MOEs calculated for chemical processing (excluding formulation) using central tendency and high-end estimates of chronic exposure to NMP are below the benchmark MOE (30) in the absence of glove use. MOEs calculated for chemical processing (excluding formulation) using central tendency and high-end estimates of chronic exposure to NMP are above the benchmark MOE (30) with incorporation of a glove protection factor (PF 10).

EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence.

Primary Strengths

EPA assessed dermal exposure to liquids using the most recent CDR data for concentration provided by industry submitters. Modeling, in the middle of the approach hierarchy, was used to estimate occupational inhalation exposure concentrations for both the unloading of NMP from bulk containers and from drums. For modeling of these air concentrations, EPA attempted to address variability in input parameters by estimating both central tendency and high-end parameter values. Additionally, EPA used Monte Carlo simulation to capture variability in input parameters. EPA expects the duration of inhalation and dermal exposure to be realistic, as the duration is based on the length of time to load NMP into drums.

Primary Limitations

The representativeness of the estimates of duration of inhalation and dermal exposure for the unloading activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. NMP concentration is reported to CDR as a range and EPA assessed only the upper end of the range since a central value cannot be ascertained for this scenario. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage is likely based on judgment. The assumed glove protection factor values are uncertain. EPA is uncertain of the accuracy of the emission factors used to estimate fugitive NMP emissions and thereby to model NMP air concentrations. The representativeness of the modeling results toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium. The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.2.4 Incorporation into Formulation, Mixture, or Reaction Product

Table 4-11. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Use of NMP in Formulations, Mixtures, or Reaction Products [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 10	Gloves PF 20	No gloves	Gloves PF 10	Gloves PF 20	
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	3.49	0.35	0.18	62	612	1198	30
		High-End	53.2	4.39	2.35	**4.1**	49	92	

[a] MOEs < 30 indicated in bold
[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction (EPA expects 100% NMP for this condition of use). High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction (EPA expects 100% NMP for this condition of use).

MOEs calculated for NMP processed into formulations, mixtures or reaction products using central tendency estimates of acute exposure to NMP are above the benchmark MOE (30). One MOE calculated using a high-end estimate of acute exposure (during maintenance, bottling, shipping) is below the benchmark MOE (30) in the absence of glove use; the MOE calculation incorporating a glove protection factor (PF 10) is above the benchmark MOE for this condition of use.

Table 4-12. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Use of NMP in Formulations, Mixtures, or Reaction Products [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b]	Chronic Exposure, AUC (hr mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 10	Gloves PF 20	No gloves	Gloves PF 10	Gloves PF 20	
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	6.2	0.63	0.32	**29**	291	570	30
		High-End	403.0	30.9	16.43	**0.45**	**6**	**11**	

[a] MOEs < 30 indicated in bold
[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction (EPA expects 100% NMP for this condition of use). High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction (EPA expects 100% NMP for this condition of use).

MOEs calculated for NMP use in formulations, mixtures or reaction products using central tendency estimates of chronic exposure to NMP are below the benchmark MOE (30) in the absence of glove use and above the benchmark MOE with the incorporation of a glove protection factor (PF 10). MOEs

calculated using a high-end estimate of chronic exposure to NMP were below the benchmark MOE (30), despite glove use (MOE = 6).

EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence.

Primary Strengths

EPA assessed dermal exposure to liquids using the most recent CDR data for concentration provided by industry submitters. Modeling, in the middle of the approach hierarchy, was used to estimate occupational inhalation exposure concentrations for the unloading of NMP from drums. For modeling of these air concentrations, EPA attempted to address variability in input parameters by estimating both central tendency and high-end parameter values. Additionally, EPA used Monte Carlo simulation to capture variability in input parameters. EPA expects the duration of inhalation and dermal exposure to be realistic, as the duration is based on the length of time to load NMP into drums. EPA assessed worker inhalation exposure during maintenance, bottling, shipping, and loading of NMP using directly applicable monitoring data, which is the highest of the approach hierarchy, taken at an adhesive formulation facility. The data quality rating for the monitoring data used by EPA is high. EPA expects the duration of inhalation and dermal exposure to be realistic for the unloading of drums, as the duration is based on the length of time to load NMP into drums.

Primary Limitations

The representativeness of the estimates of duration of inhalation and dermal exposure for the assessed activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. NMP concentration is reported to CDR as a range and EPA assessed only the upper end of the range since a central value cannot be ascertained for this scenario (NMP concentration is lower in the formulated products). Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage is likely based on professional judgement. The assumed glove protection factor values are highly uncertain. EPA estimated worker inhalation exposure concentration during the loading of NMP in solid formulations using EPA's OSHA PEL for PNOR model (U.S. EPA, 2013a), which is the lowest approach on the hierarchy. EPA did not use these inhalation exposure concentrations for the PBPK modeling because the PBPK model does not account for solids and because both the inhalation and dermal exposure potential are captured within other occupational exposure scenarios. EPA is uncertain of the accuracy of the emission factors used to estimate fugitive NMP emissions and thereby to model NMP air concentrations. For the maintenance, bottling, shipping, and loading of liquid NMP, the monitoring data consists of only 7 data points from 1 source. The representativeness of the modeling and the monitoring data toward the true distribution of inhalation concentrations for these occupational exposure scenarios is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium. The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.2.5 Application of Paints, Coatings, Adhesives and Sealants

Table 4-13. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Use of NMP in Application of Paints, Coatings, Adhesives and Sealants [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
Spray application									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	0.31	0.07	0.04	690	3000	5152	30
		High-End	24.9	4.42	2.23	**8.7**	49	97	
Roll / curtain application									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	0.30	0.06	0.03	714	3514	6880	30
		High-End	24.7	4.28	2.10	**8.8**	50	103	
Dip application									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	0.35	0.10	0.07	623	2067	2092	30
		High-End	24.8	4.36	2.18	**8.7**	50	99	
Brush application									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	0.49	0.25	0.22	440	880	1003	30
		High-End	24.8	4.40	2.22	**8.7**	49	97	

[a] MOEs < 30 are indicated in bold
[b] Central tendency means: typical air concentration (unless specified otherwise), 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case air concentration (unless specified otherwise), 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

MOEs calculated for NMP use in the application of paints, coatings, adhesives and sealants using central tendency estimates of acute exposure to NMP are above the benchmark MOE (30) with glove use (PF 5). MOEs calculated using high-end estimates of acute exposure during (spray, roll/curtain, brush and dip) application of NMP-containing paints, coatings, adhesives and sealants are below the benchmark

MOE (30) in the absence of glove use (MOE = 9). MOE calculations incorporating a glove protection factor (PF 5) were above the benchmark MOE for this condition of use.

Table 4-14. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Use of NMP in Application of Paints, Coatings, Adhesives and Sealants [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b]	Chronic Exposure, AUC (hr mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
Spray application									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	1.41	0.32	0.19	130	566	976	30
		High-End	179.6	31.1	15.70	**1.0**	**5.9**	**12**	
Roll / curtain application									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	1.36	0.28	0.14	134	661	1294	30
		High-End	178.4	30.2	14.82	**1.0**	**6.1**	**12**	
Dip application									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	1.55	0.47	0.33	118	393	556	30
		High-End	179.1	30.8	15.34	**1.0**	**5.9**	**12**	
Brush application									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	2.18	1.08	0.95	84	169	194	30
		High-End	179.5	31.1	15.62	**1.0**	**5.9**	**12**	

[a] MOEs < 30 are indicated in bold

[b] Central tendency means: typical air concentration (unless specified otherwise), 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case air concentration (unless specified otherwise), 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

MOEs calculated for NMP use in the application of paints, coatings, adhesives and sealants using central tendency estimates of chronic exposure to NMP and glove use (PF 5) are above the benchmark MOE (30). MOEs calculated for NMP use in the application of paints, coatings, adhesives and sealants using high-end estimates of chronic NMP exposure (e.g., spray, roll/curtain, brush and dip application) are below the benchmark MOE (30) despite glove use (PF 10).

EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence.

Primary Strengths

EPA assessed dermal exposure to central tendency and high-end NMP weight fractions, calculated as the 50th and 95th percentiles, respectively, from a variety of data sources with data quality ratings ranging from medium to high. To estimate inhalation exposure during spray application, EPA used directly applicable personal monitoring data, the highest of the approach hierarchy, including 26 data points. These data have a data quality rating of high. To estimate inhalation exposure during roll/curtain application, EPA used modeling, which is in the middle of the approach hierarchy. To estimate inhalation exposure during dip application, EPA used surrogate monitoring data for dip cleaning, which is in the middle of the approach hierarchy, including data from 5 sources. These data have data quality ratings of medium to high. To estimate inhalation exposure during roller / brush and syringe/bead application, EPA used modeled data from the RIVM report (RIVM, 2013), which has a data quality rating of high. The use of modeling is in the middle of the approach hierarchy. EPA used durations associated with short-term inhalation monitoring data to estimate duration of inhalation and dermal exposure during spray application.

Primary Limitations

For occupational exposure scenarios other than spray application, EPA did not find exposure duration data and assumed a high-end of 8 hours because the surrogate data or modeled values are 8-hour TWA values. EPA assumed a mid-range of 4 hours for central tendency exposure duration. The representativeness of the assumed estimates of duration of inhalation and dermal exposure for the assessed activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with minimal to no employee training or no glove usage due to the wide-spread use of paint, coating, adhesive, and sealant products. The assumed glove protection factor values are highly uncertain. The available monitoring data for spray application is from 1996 and the surrogate monitoring data used in the model for roll / curtain application is from 1994 or earlier. The extent to which these data are representative of current worker inhalation exposure potential is uncertain. The worker activities associated with the surrogate data used to assess worker inhalation exposure during dip application are not detailed for all sample points. The modeled inhalation exposure concentration during roller / brush application was obtained from RIVM (2013) and not generated by EPA. For all occupational exposure scenarios, representativeness of the monitoring data, surrogate monitoring data, or modeled data toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium. The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.2.6 Printing and Writing

Table 4-15. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Use of NMP in Printing and Writing [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b, c]	Acute Exposure, Peak blood concentration (mg/L)		MOE		Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	No gloves	Gloves PF 5	
Printing [b]							
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	0.76	0.15	286	1433	30
		High-End	2.8	0.55	78	395	
Writing [c]							
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	0.0009	0.00019	232,401	1,165,010	30
		High-End	0.0019	0.00037	116,201	582,823	

[a] MOEs < 30 are indicated in bold
[b] For printing, central tendency means: central tendency (50th percentile) air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case (95th percentile) air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.
[c] For writing, central tendency means: dermal exposure over 1 cm^2 surface area exposed [incidental contact] and central tendency NMP weight fraction. High-end means dermal over 1 cm^2 surface area exposed [incidental contact], and high-end weight NMP fraction. EPA expects inhalation exposure to NMP during writing is negligible.

MOEs calculated for NMP use in printing and writing using high-end estimates of acute exposure are above the benchmark MOE (30) in the absence of glove use. Central tendency and high-end estimates of acute exposure are above the benchmark MOE (30) with glove use (PF 5).

Table 4-16. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Use of NMP in Printing and Writing [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b, c]	Chronic Exposure, AUC (hr mg/L)		MOE		Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	No gloves	Gloves PF 5	
Printing [b]							
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	3.4	0.68	54	269	30
		High-End	19.5	3.8	**9.4**	48	
Writing [c]							
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.0016	0.000316	115,998	578,327	30
		High-End	0.0032	0.000633	57,998	289,149	

[a] MOEs < 30 are indicated in bold
[b] For printing, central tendency means: central tendency (50th percentile) air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case (95th percentile) air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.
[c] For writing, central tendency means: dermal exposure over 1 cm^2 surface area exposed [incidental contact] and central tendency NMP weight fraction. High-end means dermal over 1 cm^2 surface area exposed [incidental contact], and high-end weight NMP fraction. EPA expects inhalation exposure to NMP during writing is negligible.

MOEs calculated for NMP use in printing and writing using central tendency estimates of chronic exposure are above the benchmark MOE (30) with glove use (PF 5). One MOE calculated using a high-end estimate of chronic exposure during printing is below the benchmark MOE in the absence of glove use; the MOE calculated incorporating a glove protection factor (PF 5) is above the benchmark MOE for this condition of use. The MOE calculated for NMP use in writing using a high-end estimate of chronic exposure is above the benchmark MOE (30) in the absence of glove use.

EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence.

Primary Strengths

For printing activities, EPA assessed dermal exposure to central tendency and high-end NMP weight fractions, calculated as the 50th and 95th percentiles, respectively, from a variety of data sources with data quality ratings of high. For writing activities, EPA assessed dermal exposure to 1 to 2% NMP based on one writing product identified in the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017). For worker dermal exposure during writing, EPA determined the skin surface area dermally exposed to writing ink using a literature source with a data quality rating of high. To estimate worker inhalation exposure during printing, EPA used surrogate monitoring data, which is in the middle of the approach hierarchy. These data include 48 samples and have a data quality rating of high. EPA used durations

associated with inhalation monitoring data to estimate duration of inhalation and dermal exposure during printing activities.

Primary Limitations

For writing, EPA did not find exposure duration data and assumed a high-end of 8 hours based on the length of a full shift and a central tendency of 4 hours based on the mid-range of a shift. The representativeness of the assumed estimates of duration of inhalation and dermal exposure for the assessed printing and writing activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. For printing, skin surface areas for actual dermal contact are uncertain. EPA did not find data on glove usage. For printing activities, EPA assumed glove usage with minimal to no employee training or no glove usage due to the wide-spread use of ink products. The assumed glove protection factor values are highly uncertain. For writing activities, EPA assumed glove usage is unlikely for the use of markers, based on engineering judgement. The surrogate monitoring data used to estimate occupational inhalation exposure during printing is from 1983. The extent to which these data are representative of current worker inhalation exposure potential is uncertain. The representativeness of the surrogate monitoring data toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium. The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.2.7 Metal Finishing

Table 4-17. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Use of NMP in Metal Finishing [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
Spray application									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	9.49	1.83	0.92	**23**	118	235	30
		High-End	46.3	7.54	3.72	**4.7**	**29**	58	
Dip application									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	9.53	1.87	0.95	**23**	116	227	30
		High-End	46.2	7.49	3.67	**4.7**	**29**	59	
Brush application									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	9.69	2.01	1.09	**22**	107	198	30
		High-End	46.3	7.53	3.71	**4.7**	**29**	58	

[a] MOEs < 30 are indicated in bold

[b] Central tendency means: typical air concentration (unless specified otherwise), 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case air concentration (unless specified otherwise), 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

MOEs calculated for NMP use in metal finishing using central tendency estimates of acute exposure are above the benchmark MOE (30) with glove use (PF 5). MOEs calculated using high-end estimates of acute exposure to NMP during metal finishing (e.g., spray, dip and brush application) are below the benchmark MOE (30) in the absence of glove use; MOE calculations incorporating a glove protection factor (PF 10) are above the benchmark MOE (30) for this condition of use.

Table 4-18. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Use of NMP in Metal Finishing [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b]	Chronic Exposure, AUC (hr mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
Spray application									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	44	8.31	4.15	**4.2**	**22**	44	30
		High-End	347	53	26	**0.5**	**3.4**	**7.0**	
Dip application									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	44	8.46	4.29	**4.2**	**22**	43	30
		High-End	346	53.0	25.85	**0.5**	**3.5**	**7.1**	
Brush application									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	45	9.1	4.92	**4.1**	**20**	37	30
		High-End	347	53.3	26.14	**0.5**	**3.4**	**7.0**	

[a] MOEs < 30 are indicated in bold

[b] Central tendency means: typical air concentration (unless specified otherwise), 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case air concentration (unless specified otherwise), 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

MOEs calculated for NMP use in metal finishing (e.g., spray, dip and brush application) using central tendency estimates of chronic exposure are below the benchmark MOE (30) with glove use (PF 5). MOEs calculated using high-end estimates of chronic exposure to NMP during metal finishing (e.g., spray, dip and brush application) are below the benchmark MOE (30) with glove use (PF 10).

EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence.

Primary Strengths

EPA assessed dermal exposure to liquids using the most recent CDR data for concentration provided by industry submitters. To estimate inhalation exposure during spray application, EPA used surrogate monitoring data, which is in the middle of the approach hierarchy, including 26 data points. These data have a data quality rating of high. To estimate inhalation exposure during dip application, EPA used surrogate monitoring data for dip cleaning, which is in the middle of the approach hierarchy, including data from 5 sources. These data have data quality ratings of medium to high. To estimate inhalation exposure during brush application, EPA used modeled data from the RIVM report (RIVM, 2013), which

has a data quality rating of high. The use of modeling is in the middle of the approach hierarchy. EPA used durations associated with inhalation monitoring data to estimate duration of inhalation and dermal exposure during spray application.

Primary Limitations

For occupational exposure scenarios other than spray application, EPA did not find exposure duration data and assumed a high-end of 8 hours because the surrogate data or modeled values are 8-hour TWA values. EPA assumed a mid-range of 4 hours for central tendency exposure duration. The representativeness of the assumed estimates of duration of inhalation and dermal exposure for the assessed activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. Due to lack of data, EPA could not calculate central tendency and high-end NMP concentration in metal finishing products and used the low-end and high-end of the NMP concentration range reported in 2016 CDR. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with minimal to no employee training or no glove usage due to the potential wide-spread use of metal finishing products. The assumed glove protection factor values are highly uncertain. The available monitoring data for spray application is from 1996. The extent to which these data are representative of current worker inhalation exposure potential is uncertain. The worker activities associated with the surrogate data used to assess worker inhalation exposure during dip application are not detailed for all sample points. The modeled inhalation exposure concentration during roller/brush application was obtained from RIVM (2013) and not generated by EPA. For all occupational exposure scenarios, representativeness of the monitoring data, surrogate monitoring data, or modeled data toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium. The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.2.8 Removal of Paints, Coatings, Adhesives and Sealants

Table 4-19. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Use of NMP in the Removal of Paints, Coatings, Adhesives and Sealants [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
Miscellaneous removal									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	2.07	0.51	0.31	104	425	687	30
		High-End	36.5	7.71	4.72	**5.9**	**28**	46	
Graffiti removal									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	7.89	1.56	0.80	**27**	138	270	30
		High-End	29.2	5.07	2.55	**7.4**	43	85	

[a] MOEs < 30 are indicated in bold
[b] Central tendency means: mid-range or mean air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means high-end air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

The MOE calculated for NMP use in miscellaneous removal of paints, coatings, adhesives and sealants using a high-end estimate of acute exposure is below the benchmark MOE (30) in the absence of glove use; the MOE calculated using a high-end estimate of acute exposure with glove use (PF 10) is above the benchmark MOE. The MOE calculated for NMP use in miscellaneous removal of paints, coatings, adhesives and sealants using a central tendency estimate of acute exposure is above the benchmark MOE (30) with glove use (PF 5). MOEs calculated for NMP use in graffiti removal using central tendency and high-end estimates of acute exposure with glove use (PF = 5) are above the benchmark MOE (30).

Table 4-20. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Use of NMP in the Removal of Paints, Coatings, Adhesives and Sealants [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b]	Chronic Exposure, AUC (hr mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
Miscellaneous removal									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	5.55	1.4	0.84	33	135	218	30
		High-End	268	54	33	**0.7**	**3.4**	**5.6**	
Graffiti removal									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	36.3	7.1	3.61	**5.0**	**26**	51	30
		High-End	212	36	18	**0.9**	**5.1**	**10**	

[a] MOEs < 30 are indicated in bold

[b] Central tendency means: mid-range or mean air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means high-end air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

The MOE calculated for NMP use in miscellaneous removal of paints, coatings, adhesives and sealants using a central tendency estimate of chronic exposure is above the benchmark MOE (30) with glove use (PF 5). MOEs calculated based on high-end estimates for chronic exposure during the removal of paints, coatings, adhesives and sealants (i.e., miscellaneous removal and graffiti removal) are below the benchmark MOE (30) with glove use (PF = 10).

EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence.

Primary Strengths

EPA assessed dermal exposure to central tendency and high-end NMP weight fractions, calculated as the 50th and 95th percentiles, respectively, from a variety of data sources with data quality ratings ranging from medium to high. To estimate inhalation exposure during miscellaneous paint and coating removal, EPA used directly applicable personal monitoring data, the highest of the approach hierarchy, including data from three studies. These data have a data quality rating of high. To estimate inhalation exposure during graffiti removal, EPA used directly applicable personal monitoring data, the highest of the approach hierarchy, including 25 data points. These data have a data quality rating of high. EPA used durations associated with inhalation monitoring data to estimate duration of inhalation and dermal exposure during miscellaneous paint and coating removal.

Primary Limitations

For graffiti removal, EPA did not find data other than 8-hour TWA values. EPA assumed a high-end exposure duration equal to 8 hours and a central tendency exposure duration of 4 hours, which is the mid-range of a full shift. The representativeness of the assumed estimates of duration of inhalation and dermal exposure for the assessed activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with minimal to no employee training or no glove usage due to the wide-spread use of removal products. The assumed glove protection factor values are highly uncertain. The short-term inhalation exposure concentrations for miscellaneous removal are based on data from 1993 and the extent to which these data are representative of current worker inhalation exposure potential is uncertain. For graffiti removal, EPA used the minimum, mean, and maximum air concentrations reported by one literature source for 25 datapoints. EPA did not have these 25 data points with which to calculate 50th and 95th percentile values. The representativeness of the monitoring data toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium. The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.2.9 Cleaning

Table 4-21. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Use of NMP in Cleaning [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
Dip cleaning									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	13.7	2.62	1.32	**16**	82	163	30
		High-End	52.6	8.36	**4.07**	**4.1**	**26**	53	
Spray / wipe cleaning									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	4.88	0.99	0.52	44	218	418	30
		High-End	52.0	8.29	4.05	**4.2**	**26**	53	

[a] MOEs < 30 are indicated in bold

[b] Central tendency means: central tendency (50th percentile) air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means high-end (95th percentile) air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

MOEs calculated for NMP use in cleaning applications (e.g., dip and spray/wipe cleaning) based on central tendency estimates of acute exposure are above the benchmark MOE (30) with glove use (PF 5). MOEs calculated for NMP use in cleaning applications based on high-end estimates of acute exposure are below the benchmark MOE (30) in the absence of glove use; MOEs calculated for NMP use in cleaning applications based on high-end estimates of acute exposure incorporating a glove protection factor (PF = 10) are above the benchmark MOE.

Table 4-22. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Use of NMP in Cleaning [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [a]	Chronic Exposure, AUC (hr mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
Dip cleaning									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	64.0	12	5.99	**2.9**	**15**	31	30
		High-End	399	59	29	**0.5**	**3.1**	**6.4**	
Spray / wipe cleaning									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	22.3	4.5	2.33	**8.2**	41	79	30
		High-End	393	59	29	**0.5**	**3.1**	**6.4**	

[a] MOEs < 30 are indicated in bold
[b] Central tendency means: central tendency (50th percentile) air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means high-end (95th percentile) air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

The MOE calculated for NMP use in dip cleaning based on a central tendency estimate of chronic exposure is below the benchmark MOE (30) with glove use (PF 5); the MOE calculated for NMP use in spray/wipe cleaning based on a central tendency estimate of chronic exposure is above the benchmark MOE (30) with glove use (PF 5). MOEs calculated for NMP use in cleaning applications (i.e., dip, spray/wipe cleaning) using high-end estimates of chronic exposure and glove use (PF 10) are below the benchmark MOE.

EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence.

Primary Strengths

EPA assessed dermal exposure to central tendency and high-end NMP weight fractions, calculated as the 50th and 95th percentiles, respectively, from a variety of data sources with data quality ratings ranging from medium to high. To estimate inhalation exposure during dip cleaning, EPA used directly applicable monitoring data, which is in the highest of the approach hierarchy, including data from 5 sources. These data have data quality ratings ranging from medium to high. To estimate inhalation exposure during spray / wipe application, EPA used directly applicable monitoring data, which is in the highest of the approach hierarchy, including data from 4 sources. These data have data quality ratings ranging from medium to high.

Primary Limitations

EPA did not find exposure duration data and assumed a high-end of 8 hours based on the length of a full shift and a central tendency of 4 hours based on the mid-range of a shift. The representativeness of the assumed estimates of duration of inhalation and dermal exposure for the assessed cleaning activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with minimal to no employee training or no glove usage due to the wide-spread use of cleaning products. The assumed glove protection factor values are highly uncertain. The worker activities associated with the monitoring data used to assess inhalation exposure during dip cleaning and spray/wipe cleaning were not detailed for all samples. Where EPA could not determine the type of cleaning activities associated with a data point, EPA used the data in the estimates for both dip and spray/wipe cleaning. For both occupational exposure scenarios, the representativeness of the monitoring data toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium. The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.2.10 Commercial Automotive Servicing

Table 4-23. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Use of NMP in Commercial Automotive Servicing [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	0.35	0.21	0.20	624	1009	1090	30
		High-End	15.9	3.93	2.59	**14**	55	84	

[a] MOEs < are 30 indicated in bold

[b] Central tendency means: central tendency (50th percentile) air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means high-end (95th percentile) air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

MOEs calculated for NMP use in commercial automotive servicing based on high-end estimates of acute exposure are below the benchmark MOE (30) in the absence of glove use. MOEs calculated for NMP

use in commercial automotive servicing based on central tendency and high-end estimates of acute exposure to workers are above the benchmark MOE (30) with glove use (PF = 5).

Table 4-24. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Use of NMP in Commercial Automotive Servicing [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b]	Chronic Exposure, AUC (hr mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.92	0.6	0.53	199	319	344	30
		High-End	113	27	18	**1.6**	**6.7**	**10**	

[a] MOEs < 30 are indicated in red.
[b] Central tendency means: central tendency (50th percentile) air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means high-end (95th percentile) air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

The MOE calculated for NMP use in commercial automotive servicing (i.e., aerosol degreasing) based on high-end estimates of acute exposure is below the benchmark MOE (30) in the absence of glove use. MOEs calculated for NMP use in commercial automotive servicing based on central tendency estimates of chronic NMP exposure are below the benchmark MOE (30) with glove use (PF 10).

EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence.

Primary Strengths

EPA assessed dermal exposure to central tendency and high-end NMP weight fractions, calculated as the 50th and 95th percentiles, respectively, from a variety of data sources with data quality ratings of high. Modeling, in the middle of the approach hierarchy, was used to estimate occupational inhalation exposure concentrations. For modeling of these air concentrations, EPA attempted to address variability in input parameters by estimating both central tendency and high-end parameter values. Additionally, EPA used Monte Carlo simulation to capture variability in input parameters. EPA expects the duration of inhalation and dermal exposure to be realistic, as the duration is based on the length of time to conduct aerosol degreasing of automotive brakes.

Primary Limitations

The representativeness of the estimates of duration of inhalation and dermal exposure for the aerosol brake degreasing activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with minimal to no employee training or no glove usage due to the wide-spread use of degreasing products. The assumed glove protection factor values are highly uncertain. For the modeling of NMP air concentrations, EPA used aerosol product use rate and application frequency from one literature source (CARB, 2000) on brake servicing. The extent to which this is representative of other aerosol degreasing

applications involving NMP is uncertain. The representativeness of the modeling results toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium. The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.2.11 Laboratory Use

Table 4-25. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Use of NMP in Laboratories [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)				MOE				Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	Gloves PF 20	No gloves	Gloves PF 5	Gloves PF 10	Gloves PF 20	
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	10.4	2.0	1.0	0.50	**21**	107	214	428	30
		High-End	52.7	8.4	4.1	2.08	**4.1**	**26**	52	104	

[a] MOEs < 30 indicated in bold.
[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

MOEs calculated based on high-end estimates of acute exposure during laboratory use of NMP are below the benchmark MOE (30) in the absence of glove use. MOEs calculated for laboratory use of NMP based on high-end estimates of acute exposure are above the benchmark MOE (30), with glove use (PF 10).

Table 4-26. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Use of NMP in Laboratories [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b]	Chronic Exposure, AUC (hr mg/L)				MOE				Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	Gloves PF 20	No gloves	Gloves PF 5	Gloves PF 10	Gloves PF 20	
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	36	6.9	3.4	1.7	**5.0**	**27**	53	107	30
		High-End	400	60	29	15	**0.5**	**3.1**	**6.3**	**12**	

[a] MOEs < 30 are indicated in bold

[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

The MOE calculation based on a high-end estimate of chronic exposure to workers during laboratory use of NMP is below the benchmark MOE (30) in the absence of glove use; the MOE calculated incorporating (PF 10) glove use is below the benchmark MOE. MOEs calculated based on central tendency estimates of chronic exposure to NMP during laboratory use are above the benchmark MOE (30) with glove use (PF 10).

EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence.

Primary Strengths

EPA assessed occupational inhalation exposure using directly applicable personal monitoring data, which is the highest of the approach hierarchy, from one source with a data quality rating of medium. EPA also used a modeled inhalation exposure concentration value, which is in the middle of the approach hierarchy, from RIVM (2013). This data has a data quality rating of high. EPA determined central tendency exposure duration from the inhalation monitoring data. EPA expects the central tendency duration of inhalation and dermal exposure to be realistic, as the duration is task-based.

Primary Limitations

EPA assumed a high-end exposure duration of 8 hours based on the length of a full shift. The representativeness of the assumed estimates of duration of inhalation and dermal exposure for the assessed activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. EPA did not find NMP concentration data and assumed workers may be exposed to up to 100% NMP since NMP is a carrier chemical, and carrier chemical concentrations may be very high. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage is likely based on judgment. The assumed glove protection factor values are highly uncertain. The monitoring data used for central tendency worker inhalation exposure is only one data point from a 1996 industrial hygiene report. The extent to which these data are representative of current worker inhalation exposure potential is uncertain. The modeled high-end inhalation exposure concentration was obtained from RIVM (2013) and not

generated by EPA. The representativeness of the monitoring data and modeled exposure toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium. The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.2.12 Electronic Parts Manufacturing

Table 4-27. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Use of NMP in Electronic Parts Manufacturing [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 10	Gloves PF 20	No gloves	Gloves PF 10	Gloves PF 20	
Container handling, small containers									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	11.1	1.1	0.54	**19**	204	400	30
		High-End	46.0	3.3	1.65	**4.7**	65	131	
Container handling, drums									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	9.1	0.86	0.43	**24**	251	504	30
		High-End	46.1	3.4	1.68	**4.7**	64	128	
Fab worker									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	2.6	0.26	0.14	83	820	1598	30
		High-End	67.7	4.5	2.20	**3.2**	48	98	
Maintenance									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions	216	Central Tendency	10.1	0.95	0.47	**21**	228	458	30
		High-End	67.8	4.5	2.21	**3.2**	48	98	

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 10	Gloves PF 20	No gloves	Gloves PF 10	Gloves PF 20	
(2003; Saillenfait et al., 2002)									
Virgin NMP truck unloading									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	16.5	1.7	0.97	**13**	125	222	30
		High-End	52.8	4.1	2.10	**4.1**	52	103	
Waste truck unloading									
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	14.9	1.4	0.73	**14**	151	298	30
		High-End	47.4	3.7	1.82	**4.6**	59	119	

[a] MOEs < 30 are indicated in bold

[b] Central tendency means: central tendency (50th percentile) air concentration (for virgin NMP truck unloading and waste truck loading, EPA scaled a single 8-hour TWA value to a 4-hour TWA values), 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means high-end (95th percentile) air concentration (for virgin NMP truck unloading and waste truck loading, EPA used a single 8-hour TWA value), 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

MOEs calculated based on high-end estimates of acute exposure to workers during NMP use in electronic parts manufacturing are below the benchmark MOE (30) in the absence of glove use. High end estimates of acute exposure to workers during NMP use in electronic parts manufacturing are above the benchmark MOE with glove use (PF 10). Although the MOE calculation incorporating a glove protection factor (PF 20) is above the benchmark MOE, EPA has not found information that would indicate specific activity training (e.g., procedure for glove removal and disposal) for tasks where dermal exposure can be expected to occur. The PF 20 glove protection factor is not assumed for any central tendency or high-end estimates.

Table 4-28. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Use of NMP in Electronic Parts Manufacturing [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b]	Chronic Exposure, AUC (hr mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 10	Gloves PF 20	No gloves	Gloves PF 10	Gloves PF 20	
Container handling, small containers									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	67.4	6.31	3.21	**2.7**	**29**	57	30
		High-End	444	31.8	15.71	**0.4**	**5.8**	**12**	
Container handling, drums									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	55.1	5.13	2.56	**3.3**	36	72	30
		High-End	445	32.1	16.00	**0.4**	**5.7**	**11**	
Fab worker									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	15.6	1.57	0.80	**12**	117	228	30
		High-End	670	42.8	20.93	**0.3**	**4.3**	**8.7**	
Maintenance									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	61.1	5.65	2.81	**3.0**	32	65	30
		High-End	671	42.9	21.04	**0.3**	**4.3**	**8.7**	
Virgin NMP truck unloading									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	78.1	7.83	4.36	**2.3**	**23**	42	30
		High-End	400	29.2	14.79	**0.5**	**6.3**	**12.4**	
Waste truck unloading									
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	70.22	6.45	3.28	**2.6**	**28**	56	30
		High-End	356	26.00	12.84	**0.5**	**7.0**	**14.3**	

[a] MOEs < 30 indicated in bold

[b] Central tendency means: central tendency (50th percentile) air concentration (for virgin NMP truck unloading and waste truck loading, EPA scaled a single 8-hour TWA value to a 4-hour TWA values), 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means high-end (95th percentile) air concentration (for

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b]	Chronic Exposure, AUC (hr mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 10	Gloves PF 20	No gloves	Gloves PF 10	Gloves PF 20	
virgin NMP truck unloading and waste truck loading, EPA used a single 8-hour TWA value), 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.									

MOEs calculated based on high-end estimates of chronic exposure to workers during NMP use in electronic parts manufacturing (i.e., handling, unloading, maintenance and fab worker) are below the benchmark MOE (30) regardless of glove use. Although the MOE calculation incorporating a glove protection factor (PF 20) is above the benchmark MOE, EPA has not found information that would indicate specific activity training (e.g., procedure for glove removal and disposal) for tasks where dermal exposure can be expected to occur. The PF 20 glove protection factor is not assumed for any central tendency or high-end estimates.

4.2.2.13 Soldering

Table 4-29. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Use of NMP in Soldering [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	0.15	0.03	0.02	1436	7187	14376	30
		High-End	0.97	0.19	0.10	222	1120	2242	
[a] MOEs < 30 are indicated in bold [b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.									

The MOE calculated for NMP use in soldering based on high-end estimates of acute exposure is above the benchmark MOE (30) in the absence of glove use (MOE = 222); the MOE calculated based on central tendency estimates of acute exposure to workers during NMP use in soldering is above the benchmark MOE with glove use (PF 5).

Table 4-30. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Use of NMP in Soldering [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b]	Chronic Exposure, AUC (hr mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.68	0.14	0.07	270	1350	2701	30
		High-End	6.8	1.36	0.68	**27**	135	270	

[a] MOEs < 30 indicated in bold
[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

The MOE calculated based on a high-end estimate of chronic exposure to workers from NMP use in soldering is below the benchmark MOE (30) in the absence of glove use (MOE = 27); the MOE calculated based on a high-end estimate of chronic exposure to workers incorporating a glove protection factor (PF 10) is above the benchmark MOE. The MOE calculated based on a central tendency estimate of chronic exposure to workers with glove use (PF 5) is above the benchmark MOE.
EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence.

Primary Strengths
EPA assessed dermal exposure to central tendency and high-end NMP weight fractions, calculated as the 50th and 95th percentiles, respectively, from the data provided by SIA (2019), which has a data quality rating of high. EPA used directly applicable inhalation monitoring data, which is the highest of the approach hierarchy, to estimate worker inhalation exposure during a variety of semiconductor manufacturing tasks. These data include over one hundred data points and have a data quality rating of high.

Primary Limitations
The SIA (2019) monitoring data were provided as 8-hour or 12-hour TWA values. EPA assumed 8 or 12 hours as the high-end exposure duration and mid-range of 4 or 6 hours as the central tendency exposure duration. The representativeness of the estimates of duration of inhalation and dermal exposure for the assessed activities toward the true distribution of duration for all worker activities in this occupational exposure scenario beyond semiconductor manufacturing is uncertain. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage is likely based on judgment. The assumed glove protection factor values are highly uncertain. The majority of the data points in SIA (2019) were non-detect for NMP and, for these samples, EPA used the LOD/2 to calculate central tendency and high-end inhalation exposure concentration values. Due to the high amount of non-detect results, this method may result in bias. The representativeness of the monitoring data for semiconductor manufacturing toward the true distribution of inhalation concentrations for all worker activities in this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium. The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.2.14 Fertilizer Application

Table 4-31. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Use of NMP in Fertilizer Application [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	0.15	0.14	0.13	1430	1587	1604	30
		High-End	2.9	0.70	0.42	74	310	510	

[a] MOEs < 30 are indicated in bold

[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

The MOEs calculated for NMP use in fertilizer application based on high-end estimates of acute exposure for workers are above the benchmark MOE (30) in the absence of glove use. Central tendency and high-end estimates of acute exposure to workers during the use of NMP in fertilizer application are above the benchmark MOE with glove use (PF 5).

Table 4-32. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Use of NMP in Fertilizer Application [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b]	Chronic Exposure, AUC (hr mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.66	0.60	0.59	279	307	311	30
		High-End	20.6	4.9	2.9	**8.9**	38	62	

[a] MOEs < 30 are indicated in bold
[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

The MOE calculated for NMP use in fertilizer application based on a high-end estimate of chronic exposure to workers is below the benchmark MOE (30) in the absence of glove use (MOE = 9). The MOEs calculated based on central tendency and high-end estimates of chronic exposure to workers incorporating a glove protection factor (PF = 5) is above the benchmark MOE.

EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence.

Primary Strengths

EPA assessed dermal exposure to 0.1 to 7% NMP, based on data from public comments and literature, which have data quality ratings of high. EPA assessed occupational inhalation exposure during fertilizer application using a modeled inhalation exposure concentration value, which is in the middle of the approach hierarchy, from RIVM (2013). This data has a data quality rating of high.

Primary Limitations

EPA did not find exposure duration data and assumed a high-end of 8 hours based on the length of a full shift and a central tendency of 4 hours based on the mid-range of a shift. The representativeness of the assumed estimates of duration of inhalation and dermal exposure toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with minimal to no employee training or no glove usage due to the commercial nature of this use. The assumed glove protection factor values are highly uncertain. The modeled inhalation exposure concentration was obtained from RIVM (2013) and not generated by EPA. The representativeness of the modeled exposure toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium. The studies that support the health concerns for

adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.2.15 Wood Preservatives

Table 4-33. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Use of NMP in Wood Preservatives [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)		MOE		Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	No gloves	Gloves PF 5	
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	0.34	0.22	635	1003	30
		High-End	0.51	0.20	426	1099	

[a] MOEs < 30 indicated in bold
[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

The MOE calculated based on a high-end estimate of acute exposure to workers from NMP use in wood preservatives is above the benchmark MOE (30) in the absence of glove use. The MOEs calculated based on central tendency and high-end estimates of acute exposure to workers from NMP use in wood preservatives are above the benchmark MOE (30) with glove use (PF 5).

Table 4-34. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Use of NMP in Wood Preservatives [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b]	Chronic Exposure, AUC (hr mg/L)		MOE		Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	No gloves	Gloves PF 5	
REPRODUCTIVE EFFECTS Decreased Fertility (Exxon, 1991)	183	Central Tendency	1.5	0.95	122	194	30
		High-End	3.5	1.4	52	135	

[a] MOEs < 30 are indicated in bold
[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

The MOE calculated based on a high-end estimate of chronic exposure to workers from NMP use in wood preservatives is above the benchmark MOE (30) in the absence of glove use. MOEs for NMP use in wood preservatives based on central tendency and high-end estimates of chronic exposure to workers are above the benchmark MOE with glove use (PF 5).

EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence.

Primary Strengths

EPA assessed dermal exposure to 1% NMP, based on one wood preservative product identified in the *Use and Market Profile for N-Methylpyrrolidone* (Abt, 2017). EPA assessed occupational inhalation exposure during wood preservative application using a modeled inhalation exposure concentration value, which is in the middle of the approach hierarchy, from RIVM (2013). This data has a data quality rating of high.

Primary Limitations

EPA did not find exposure duration data and assumed a high-end of 8 hours based on the length of a full shift and a central tendency of 4 hours based on the mid-range of a shift. The representativeness of the assumed estimates of duration of inhalation and dermal exposure toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with minimal to no employee training or no glove usage due to the commercial nature of this use. The assumed glove protection factor values are highly uncertain. The modeled inhalation exposure concentration was obtained from RIVM (2013) and not generated by EPA. The representativeness of the modeled exposure toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium. The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.2.16 Recycling and Disposal

Table 4-35. Non-Cancer Risk Estimates for Acute Exposures Following Occupational Recycling and Disposal of NMP [a]

Health Effect, Endpoint and Study	Acute POD, Cmax (mg/L)	Exposure Level [b]	Acute Exposure, Peak blood concentration (mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	Central Tendency	3.8	0.76	0.38	56	283	562	30
		High-End	9.4	1.9	0.96	**23**	114	225	

[a] MOEs < 30 are indicated in bold

[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

The MOE calculated based on a high-end estimate of acute exposure to workers from recycling and disposal of NMP is below the benchmark MOE (30) in the absence of glove use; the MOE calculated based on central tendency estimates of acute exposure to workers from recycling and disposal of NMP is above the benchmark MOE in the absence of glove use. The MOE calculated based on a high-end estimate of acute exposure to workers from recycling and disposal of NMP is above the benchmark MOE with glove use (PF 5).

Table 4-36. Non-Cancer Risk Estimates for Chronic Exposures Following Occupational Recycling and Disposal of NMP [a]

Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Exposure Level [b]	Chronic Exposure, AUC (hr mg/L)			MOE			Benchmark MOE (= Total UF)
			No gloves	Gloves PF 5	Gloves PF 10	No gloves	Gloves PF 5	Gloves PF 10	
REPRODUCTIVE EFFECTS	183	Central Tendency	7.9	1.57	0.79	**23**	116	232	30

Decreased Fertility (Exxon, 1991)		High-End	21.6	4.2	2.14	**8.5**	43	86	

[a] MOEs < 30 are indicated in bold
[b] Central tendency means: typical air concentration, 1-hand dermal (445 cm^2 surface area exposed), and central tendency NMP weight fraction. High-end means worst-case air concentration, 2-hand dermal (890 cm^2 surface area exposed), and high-end weight NMP fraction.

MOEs calculated based on central tendency and high-end estimates of chronic exposure to workers from recycling and disposal of NMP are below the benchmark MOE (30) in the absence of glove use. MOEs calculated based on central tendency and high-end estimates of chronic exposure to workers from recycling and disposal of NMP are above the benchmark MOE with glove use (PF = 5).

EPA considered the assessment approach, the quality of the data, and uncertainties to determine the level of confidence.

Primary Strengths

Modeling, in the middle of the approach hierarchy, was used to estimate occupational inhalation exposure concentrations for both the unloading of NMP from bulk containers and from drums. For modeling of these air concentrations, EPA attempted to address variability in input parameters by estimating both central tendency and high-end parameter values. Additionally, for modeling of air concentrations during the unloading of drums, EPA used Monte Carlo simulation to capture variability in input parameters. EPA expects the duration of inhalation and dermal exposure to be realistic for the unloading activities, as the durations are based on the length of time to unload NMP from specific container sizes (i.e., tank trucks, rail cars, and drums).

Primary Limitations

The representativeness of the estimates of duration of inhalation and dermal exposure for the unloading activities toward the true distribution of duration for all worker activities in this occupational exposure scenario is uncertain. EPA did not find NMP concentration data and assumed waste NMP may contain very little impurities and be up to 100% NMP. Skin surface areas for actual dermal contact are uncertain. EPA did not find data on the use of gloves for this occupational exposure scenario and assumed glove usage with basic employee training is likely based on judgment. The assumed glove protection factor values are highly uncertain. For the modeling of NMP air concentrations, EPA is uncertain of the accuracy of the emission factors used to estimate fugitive NMP emissions and thereby estimate worker inhalation exposure concentration. The representativeness of the modeling results toward the true distribution of inhalation concentrations for this occupational exposure scenario is uncertain.

Overall Confidence

Considering the overall strengths and limitations, the overall confidence of the PBPK input parameters for this occupational exposure scenario is medium. The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.3 Risk Estimation for Exposures to NMP for Occupational Non-Users

The following table presents the risk estimates for chronic inhalation exposures to ONUs for reproductive effects using estimated air concentrations from workplaces that use NMP in each OES. ONUs are not assumed to be exposed via dermal contact with liquid NMP because they do not have direct dermal contact with liquid chemicals, see section 2.4.1.1. ONUs are not assumed to be wearing a respirator. Calculated MOE values that are below the benchmark MOE (30), indicate a risk concern (shown in bold and shaded grey). Risk estimates for acute inhalation exposures to ONUs for developmental effects in pregnant women from workplaces that use NMP are not shown because the MOEs are all greater than the benchmark MOE of 30. The highest exposure scenario for ONUs is paint removers – miscellaneous stripping with an 8 hr TWA air concentration of 64 mg/m^3 and the peak blood concentration is 1.53 mg/L and for the developmental effects with the POD peak blood concentration of 216 mg/L the MOE is 141, above the benchmark MOE of 30.

Table 4-37. ONU Risk Estimates based on Adverse Reproductive Effects (Decreased Fertility) from Chronic NMP Exposures [a]

Occupational Exposure Scenario [a]	Exposure Level [b]	Chronic Exposure [c], AUC (hr mg/L)	MOEs [d]
Manufacturing of NMP	Central Tendency	0.011	16344
	High-End	0.31	587
Repackaging	Central Tendency	0.011	16344
	High-End	0.31	587
Chemical Processing, Excluding Formulation	Central Tendency	0.016	11255
	High-End	0.055	3343
Incorporation into Formulation, Mixture, or Reaction Product	Central Tendency	0.016	11255
	High-End	2.63	70
Application of Paints, Coatings, Adhesives, and Sealants-- Spray Application	Central Tendency	0.052	3525
	High-End	0.93	197
Application of Paints, Coatings, Adhesives, and Sealants--Roll/curtain	Central Tendency	0.0059	30904
	High-End	0.052	3522
Application of Paints, Coatings, Adhesives, and Sealants--Dip	Central Tendency	0.19	944
	High-End	0.57	321
Application of Paints, Coatings, Adhesives, and Sealants--Brush	Central Tendency	0.81	226
	High-End	0.85	215
Printing	Central Tendency	0.0017	108142

Occupational Exposure Scenario [a]	Exposure Level [b]	Chronic Exposure [c], AUC (hr mg/L)	MOEs [d]
	High-End	0.037	5001
Writing	Central Tendency	0.000032	5784391
	High-End	0.00032	580007
Metal finishing - spray application	Central Tendency	0.053	3428
	High-End	0.94	195
Metal finishing - dip	Central Tendency	0.20	937
	High-End	0.58	316
Metal finishing - brush	Central Tendency	0.81	226
	High-End	0.86	213
Paint and coating removal - misc. removal	Central Tendency	0.32	566
	High-End	13	**14**
Paint and coating removal - graffiti removal	Central Tendency	0.20	920
	High-End	0.93	196
Dip cleaning	Central Tendency	0.20	934
	High-End	0.58	314
Spray / Wipe Cleaning	Central Tendency	0.20	922
	High-End	0.71	258
Commercial Automotive Servicing	Central Tendency	0.49	374
	High-End	8.91	**21**
Laboratory Use	Central Tendency	0.010	17565
	High-End	0.81	225
Electronic Parts Manufacturing--Electronics (Small Container Handling)	Central Tendency	0.15	1225
	High-End	0.21	859
Electronic Parts Manufacturing--Electronics (Container Handling, Drums)	Central Tendency	0.0043	42649
	High-End	0.50	368
Electronic Parts Manufacturing--Electronics (Fab worker)	Central Tendency	0.041	4502
	High-End	0.16	1137

Occupational Exposure Scenario [a]	Exposure Level [b]	Chronic Exposure [c], AUC (hr mg/L)	MOEs [d]
Electronic Parts Manufacturing--Electronics (Maintenance)	Central Tendency	0.0064	28624
	High-End	0.25	739
Electronic Parts Manufacturing--Electronics (Virgin NMP Truck Unloading)	Central Tendency	0.94	195
	High-End	0.99	184
Section 2.4.1.2.12 – Electronic Parts Manufacturing--Electronics (Waste Truck Unloading)	Central Tendency	0.14	1313
	High-End	0.17	1097
Soldering	Central Tendency	0.000025	7224526
	High-End	0.00063	289802
Fertilizer Application	Central Tendency	0.58	315
	High-End	1.1	171
Wood preservative	Central Tendency	0.81	226
	High-End	0.84	219
Recycling and Disposal	Central Tendency	0.011	16530
	High-End	0.091	2007

[a] Use of PPE is not assumed for ONUs
[b] Central tendency means: typical air concentration for most scenarios. High-end means worst-case air concentration for most scenarios. ONUs are not expected to have direct contact with NMP-containing liquids (see Section 2.4.1.1).
[c] POD blood concentration =183 mg/L (AUC)
[d] Benchmark MOE = 30; MOEs < 30 are indicated in bold

6004
6005

4.2.4 Risk Estimation for Acute Exposures from Consumer Use of NMP

The following sections present the risk estimates for acute dermal and inhalation exposures following consumer use of NMP in each condition of use. Calculated MOE values that are below the benchmark MOE (30), indicate a consumer safety concern (shown in red and bold)

4.2.4.1 Adhesives and Sealants

Table 4-38. Non-Cancer Risk Estimates for Acute Exposures Following Consumer Use of NMP in Adhesives and Sealants

Exposure Scenario[1]	Health Effect, Endpoint and Study	POD (peak blood concentration, mg/L)	Women childbearing age Exposure, peak blood concentration, Cmax (mg/L)	MOE	Benchmark MOE (Total UF)
Sealants Medium Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	0.011	19115	30
Sealants High Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	0.070	3086	30
Adhesives Medium Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	1.238	174	30
Adhesives High Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	5.623	38	30

All MOEs calculated using a high-end estimate for acute exposure to consumers following use of NMP-containing adhesives and sealants are above the benchmark MOE (30).
for these conditions of use.

Overall Confidence

The adhesives scenarios and the sealants scenarios are based on corresponding publicly available consumer product data, specifically the weight fractions and the amount of product used and duration of use from consumer survey data. EPA has a high confidence in these parameters for representing the adhesives and sealants consumer use scenarios.

EPA has a high confidence in the Consumer Exposure Model (CEM), its appropriate use for semi-volatile chemicals such as NMP in estimating air concentrations based on the consumer use, activity patterns, and NMP physical-chemical properties. The emission rate used in CEM for the adhesives scenario and sealants scenario was estimated since product-specific emission from chamber studies was not available. EPA has high confidence in the emission rate estimate based on physical-chemical properties.

The input parameters for estimating the consumer's internal dose using the PBPK model are: the estimated air concentration resulting from product use as predicted by CEM, the dermal contact time (based on the duration of product use) and the weight fraction of the product.

EPA has a high confidence in the input parameters estimating the adhesive scenario and the sealants scenario.

The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.4.2 Adhesives Removers

Table 4-39. Non-Cancer Risk Estimates for Acute Exposures Following Consumer Use of NMP in the Removal of Adhesives

Exposure Scenario[1]	Health Effect, Endpoint and Study	POD (peak blood concentration, mg/L)	Women childbearing age Exposure, peak blood concentration, Cmax (mg/L)	MOE	Benchmark MOE (Total UF)
Medium Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	1.292	167	30
High Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions	216	5.957	36	30

Exposure Scenario[1]	Health Effect, Endpoint and Study	POD (peak blood concentration, mg/L)	Women childbearing age Exposure, peak blood concentration, Cmax (mg/L)	MOE	Benchmark MOE (Total UF)
	(2003; Saillenfait et al., 2002)				

All MOEs calculated using high-end estimates for acute exposure to consumers from use of NMP-containing adhesive removal products are above the benchmark MOE (30).

Overall Confidence

The adhesives remover scenario is based on corresponding publicly available consumer product data, specifically the weight fractions and the amount of product used and duration of use from consumer survey data. EPA has a high confidence in these parameters for representing the adhesives remover consumer use scenarios.

EPA has a high confidence in the Consumer Exposure Model (CEM), its appropriate use for semi-volatile chemicals such as NMP in estimating air concentrations based on the consumer use, activity patterns, and NMP physical-chemical properties. The emission rate used in CEM for the adhesive remover scenario was estimated since product-specific emission from chamber studies was not available. EPA has high confidence in the emission rate estimate based on physical-chemical properties.

The input parameters for estimating the consumer's internal dose using the PBPK model are: the estimated air concentration resulting from product use as predicted by CEM, the dermal contact time (based on the duration of product use) and the weight fraction of the product.

EPA has a high confidence in the input parameters estimating the adhesives remover scenario.

The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.4.3 Auto Interior Liquid and Spray Cleaners

Table 4-40. Non-Cancer Risk Estimates for Acute Exposures Following Consumer Use of NMP in Auto Interior Liquid and Spray Cleaners

Exposure Scenario[1]	Health Effect, Endpoint and Study	POD (peak blood concentration, mg/L)	Women childbearing age Exposure, peak blood concentration, Cmax (mg/L)	MOE	Benchmark MOE (Total UF)
Auto Interior Liquid Cleaner Medium Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	0.256	844	30
Auto Interior Liquid Cleaner High Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	4.355	50	30
Auto Interior Spray Cleaner Medium Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	0.093	2323	30
Auto Interior Spray Cleaner High Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	0.183	1180	30

All MOEs calculated using high-end estimates for acute exposure to consumers from the use of NMP-containing auto interior (liquid and spray) cleaners are above the benchmark MOE (30).

Overall Confidence

The auto interior liquid cleaner scenario and the auto interior spray cleaner scenario are based on corresponding publicly available consumer product data, specifically the weight fractions and the amount of product used and duration of use from consumer cleaner/degreaser survey data. EPA has a medium to high confidence in these parameters for representing the auto interior liquid cleaner scenario and the auto interior spray cleaner consumer use scenarios.

EPA has a high confidence in the Consumer Exposure Model (CEM), its appropriate use for semi-volatile chemicals such as NMP in estimating air concentrations based on the consumer use, activity patterns, and NMP physical-chemical properties. The emission rate used in CEM for the auto interior liquid cleaner scenario and the auto interior spray cleaner scenario was estimated since product-specific emission from chamber studies was not available. EPA has high confidence in the emission rate estimate based on physical-chemical properties.
The input parameters for estimating the consumer's internal dose using the PBPK model are: the estimated air concentration resulting from product use as predicted by CEM, the dermal contact time (based on the duration of product use) and the weight fraction of the product.

EPA has a medium to high confidence in the input parameters estimating the auto interior liquid cleaner scenario and the auto interior spray cleaner scenario.

The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.4.4 Cleaners/Degreasers, Engine Cleaner/Degreaser and Spray Lubricant

Table 4-41. Non-Cancer Risk Estimates for Acute Exposures Following Consumer Use of NMP in Cleaners/Degreasers, Engine Cleaner/Degreaser and Spray Lubricant

Exposure Scenario[1]	Health Effect, Endpoint and Study	POD (peak blood concentration, mg/L)	Women childbearing age Exposure, peak blood concentration, Cmax (mg/L)	MOE	Benchmark MOE (Total UF)
Cleaners/Degreasers Medium Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	1.033	209	30
Cleaners/Degreasers High Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	13.40	**16**	30
Engine Cleaner/Degreaser Medium Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions	216	1.682	128	30

Exposure Scenario[1]	Health Effect, Endpoint and Study	POD (peak blood concentration, mg/L)	Women childbearing age Exposure, peak blood concentration, Cmax (mg/L)	MOE	Benchmark MOE (Total UF)
	(2003; Saillenfait et al., 2002)				
Engine Cleaner/Degreaser High Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	16.46	**13**	30
Spray Lubricant Medium Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	0.332	651	30
Spray Lubricant High Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	2.853	76	30

MOEs calculated based on high end estimates for acute exposure to consumers from the use of NMP-containing cleaners/degreasers are below the benchmark MOE (30); $MOE_{cleaners/degreaser} = 16$, $MOE_{engine\ cleaner/degreaser} = 13$).

Overall Confidence

The cleaner/degreaser scenario and the engine cleaner/degreaser scenario are based on corresponding publicly available consumer product data, specifically the weight fractions and the amount of product used and duration of use from consumer survey data. EPA has a high confidence in these parameters for representing the cleaner/degreaser and engine cleaner/degreaser consumer use scenarios.

EPA has a high confidence in the Consumer Exposure Model (CEM), its appropriate use for semi-volatile chemicals such as NMP in estimating air concentrations based on the consumer use, activity patterns, and NMP physical-chemical properties. The emission rate used in CEM for the cleaner/degreaser scenario and engine cleaner/degreaser scenario was estimated since product-specific

emission from chamber studies was not available. EPA has high confidence in the emission rate estimate based on physical-chemical properties.

The input parameters for estimating the consumer's internal dose using the PBPK model are: the estimated air concentration resulting from product use as predicted by CEM, the dermal contact time (based on the duration of product use) and the weight fraction of the product.

EPA has a high confidence in the input parameters estimating the cleaner/degreaser scenario and the sealants scenario.

The studies that support the health concerns for adverse developmental effects following acute exposure and adverse reproductive effects following chronic exposure are described above in Section 3.2. Overall, EPA has high confidence in the health endpoints and PODs selected for acute and chronic risk characterization. Section 3.2.6 describes the justification for this confidence rating.

4.2.4.5 Paints and Arts and Craft Paint

Table 4-42. Non-Cancer Risk Estimates for Acute Exposures Following Consumer Use of NMP in Paint and Arts and Craft Paint

Exposure Scenario[1]	Health Effect, Endpoint and Study	POD (peak blood concentration, mg/L)	Women childbearing age Exposure, peak blood concentration, Cmax (mg/L)	MOE	Benchmark MOE (Total UF)
Paints Medium Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	0.374	578	30
Paints High Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	1.422	152	30
Arts and Crafts Paints Medium Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	0.071	3034	30

Exposure Scenario[1]	Health Effect, Endpoint and Study	POD (peak blood concentration, mg/L)	Women childbearing age Exposure, peak blood concentration, Cmax (mg/L)	MOE	Benchmark MOE (Total UF)
Arts and Crafts Paints High Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	0.222	974	30

All MOEs calculated using high-end estimates of acute exposure to consumers from the use of NMP-containing paints (including those used in arts and crafts) are above the benchmark MOE (30).

4.2.4.6 Stains, Varnishes, Finishes (Coatings)

Table 4-43. Non-Cancer Risk Estimates for Acute Exposures Following Consumer Use of NMP in Stains, Varnishes, Finishes (Coatings)

Exposure Scenario[1]	Health Effect, Endpoint and Study	POD (peak blood concentration, mg/L)	Women childbearing age Exposure, peak blood concentration, Cmax (mg/L)	MOE	Benchmark MOE (Total UF)
Medium Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	0.341	633	30
High Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	1.947	111	30

All MOEs calculated using high-end estimates of acute exposure to consumers from the use of NMP-containing stains, varnishes and finishes (coatings) are above the benchmark MOE (30).

4.2.4.7 Paint Removers

Table 4-44. Non-Cancer Risk Estimates for Acute Exposures Following Consumer Use of NMP in Paint Removers

Exposure Scenario[1]	Health Effect, Endpoint and Study	POD (peak blood concentration, mg/L)	Women childbearing age Exposure, peak blood concentration, Cmax (mg/L)	MOE	Benchmark MOE (Total UF)
Medium Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	2.02	107	30
High Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	10.02	**22**	30

One MOE calculated using a high-end estimate for acute exposure to consumers from the use of NMP-containing paint removers is below the benchmark MOE (30); $MOE_{\text{High Intensity Use}} = 22$.

4.2.4.8 Risks to Bystanders

Table 4-45. Risk Estimates to Adult Bystanders for Acute Exposures Following Consumer Use of NMP in Degreasing or Engine Degreasing

Exposure Scenario[1]	Health Effect, Endpoint and Study	POD (peak blood concentration, mg/L)	Women childbearing age Exposure, peak blood concentration, Cmax (mg/L)	MOE	Benchmark MOE (Total UF)
Cleaners/Degreasers High-Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	4.06	53	30
Engine Cleaner/Degreaser High Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	5.55	39	30

Table 4-46. Risk Estimates for Adverse Developmental Effects (Increased Resorptions/Fetal Mortality) from Acute Exposure to Bystanders via Consumer Use of NMP in Degreasing or Engine Degreasing

Exposure Scenario[1]	Health Effect, Endpoint and Study	POD (peak blood concentration, mg/L)	Child (3-5yrs) Exposure, peak blood concentration, Cmax (mg/L)	MOE	Benchmark MOE (Total UF)
Cleaners/Degreasers High-Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	4.76	45	30
Engine Cleaner/Degreaser High Intensity Use	DEVELOPMENTAL EFFECTS Increased Fetal Resorptions (2003; Saillenfait et al., 2002)	216	6.51	33	30

All MOEs calculated using high-end estimates of acute exposure to bystanders from the use of NMP-containing degreasers or engine degreasers are above the benchmark MOE (30).

4.3 Assumptions and Key Sources of Uncertainty

4.3.1 Assumptions and Uncertainties in Occupational Exposure Assessment

Assumptions and sources of uncertainty for occupational exposure estimates are described in greater detail in Section 2.4.1.4. Sources of uncertainty and overall confidence in occupational exposure estimates vary across occupational exposure scenarios. Overall confidence in exposure estimates for specific conditions of use are described in Section 4.2.2.

A peer-reviewed PBPK model allows EPA to estimate aggregate exposures from simultaneous dermal and inhalation and vapor-through-skin exposures with relatively high confidence. The body weight parameter is related to all of these three routes. The assumed values for human body weight have relatively lower uncertainties, and the median values used may underestimate exposures at the high-end of PBPK exposure results.

Estimates of dermal exposure rely on a set of assumptions that introduce uncertainty because no data are available for many parameters. The types of data and assumptions used to estimate exposure for each exposure scenario is summarized in Table 4-48. Parameters that rely on such assumptions include glove use and effectiveness, durations of contact with liquid, skin surface areas for contact with liquids. For many OESs, the high-end surface area assumption of contact over the full area of two hands likely overestimates exposures. EPA has more confidence in dermal exposure parameters that are supported by data, such as NMP concentrations in formulas. There is also uncertainty around the impact of vapors being trapped next to the skin during glove use. For most of the assumptions made for exposure parameters and other sources of uncertainty, EPA does not have enough information to determine whether most of these assumptions may overestimate or underestimate exposures. The NMP concentrations in liquid used in dermal exposure predictions are likely to have a relatively low impact (less than an order of magnitude, or factor of 10) on overestimation or underestimation of exposure.

Estimates of inhalation and vapor-through-skin exposures also rely on various assumptions that introduce uncertainty. The specific types of data sources used Estimated air concentrations are based on monitoring data where available and based on deterministic or probabilistic modeling for exposure scenarios lacking monitoring data. Table 4-47 summarizes the types of data used to estimate air concentrations for each occupational exposure scenario. The principal limitation of the air concentration monitoring data is the uncertainty in the representativeness of the data. EPA identified a limited number of exposure studies and data sets that provided data for facilities or job sites where NMP was used. Some of these studies primarily focused on single sites. This small sample pool introduces uncertainty as it is unclear how representative the data for a specific end use are for all sites and all workers across the US. Limited monitoring datasets precluded EPA from describing actual parameter distributions. In most scenarios where data were available, EPA did not find enough data to determine complete statistical distributions to identify 50th and 95th percentile exposures. In the absence of percentile data for monitoring, the means or midpoint of the range serve as substitutes for 50th percentiles of the actual distributions and high ends of ranges serve as substitutes for 95th percentiles of the actual distributions. The effects of limited air monitoring datasets of unknown representativeness on the occupational exposure assessment are unknown. They may result in either over or underestimation of exposures depending on the actual distribution.

Where air monitoring data were not available, exposure was estimated based on deterministic or probabilistic modeling. Modeling approaches used to estimate air concentrations also have uncertainties. Parameter values used in models did not all have distributions known to represent the modeled scenario. It is also uncertain whether the model equations generate results that represent actual workplace air concentrations. Some activity-based modeling does not account for exposures from other activities. Additional model-specific uncertainties are included below. In general, the effects of model-specific uncertainties on the exposure estimates are unknown, as the uncertainties may result in either over or underestimation on exposures depending on the actual distributions of each of the model input parameters.

Table 4-47. Summary of Occupational Air Concentration Estimate Approaches

Exposure Scenario	Work Activity	Worker Personal Breathing Zone Monitoring Data	Modeling: Deterministic Worker [a]	Modeling: Probabilistic Worker (X) Near Field/ ONU Far Field (X [e])	Potential ONU-related Data
1. Manufacturing	Loading NMP into bulk containers		X		
	Loading NMP into drums			X	
2. Repackaging	Unloading NMP from bulk containers		X		
	Unloading NMP from drums			X	
3. Chemical Processing, Excluding Formulation	Unloading NMP from drums			X	
4. Incorporation into Formulation, Mixture, or Reaction Product	Unloading liquid NMP from drums			X	
	Maintenance, bottling, shipping, loading	X (7 samples)			^ (area monitoring) [c]
5. Metal finishing	Spray application	X (26 samples)			^ (area monitoring) [c]
	Dip application	X (138 samples)	X [b]		
	Brush application		X [b]		

Exposure Scenario	Work Activity	Worker Personal Breathing Zone Monitoring Data	Modeling: Deterministic Worker [a]	Modeling: Probabilistic Worker (X) Near Field/ ONU Far Field (X [e])	Potential ONU-related Data
6. Removal of Paints, Coatings, Adhesives and Sealants	Miscellaneous paint, coating, adhesive, and sealant removal	X (unknown) [d]			
	Graffiti removal	X (25 samples)			
7. Application of Paints, Coatings, Adhesives and Sealants	Spray application	X (26 samples)			X (area monitoring) [c]
	Roll/ curtain application		X		
	Dip application	X (138 samples)	X [b]		
	Roller/ brush and syringe/ bead application		X [b]		
8. Electronic Parts Manufacturing	Container handling (small containers);	X (14 samples)			
	Container handling, drums	X (10 samples)			
	Fab worker	X (28 samples)			^ (area monitoring) [c]
	Maintenance	X (36 samples)			
	Virgin NMP truck unloading	X (1 sample)			
	Waste truck loading	X (1 sample)			
9. Printing and Writing	Printing	X (48 samples)			
	Writing	Inhalation not assessed			
10. Soldering	Soldering	Inhalation not assessed			
11. Commercial Automotive Servicing				X [e]	

Exposure Scenario	Work Activity	Worker Personal Breathing Zone Monitoring Data	Modeling: Deterministic Worker [a]	Modeling: Probabilistic Worker (X) Near Field/ ONU Far Field (X [e])	Potential ONU-related Data
12. Laboratory Use	Laboratory use	X (1 sample)	X [b]		
13. Cleaning	Dip cleaning / degreasing	X (138 samples)	X [b]		
	Spray / wipe cleaning	X (105 samples)	X [b]		
14. Fertilizer application	Spray application		X [b]		
15. Wood preservatives	Brush application		X [b]		
16. Recycling and disposal	Unloading NMP from bulk containers		X		
	Unloading NMP from drums			X	

a – The deterministic modeling approaches estimate worker exposures.
b – These modeling estimates are from literature (RIVM, 2013). Other modeling estimates are from modeling performed by EPA.
c – While area monitoring data were identified, there is some uncertainty about the representativeness of these data for ONU exposures for these specific exposure scenarios because of the intended sample population and the selection of the specific monitoring location.
d – The number of samples is unknown. The data source only presented the range.
e – This modeling includes Near Field modeling for worker exposures and Far Field modeling for ONU exposures. Far Field modeling results are not included in the RE but are included in *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment* (U.S. EPA, 2019r).

Table 4-48. Summary of Worker Dermal Parameter Estimate Approaches

Exposure Scenario	Work Activity	NMP weight fraction in the liquid product	Total skin surface area of hands in contact with the liquid product[b]	Duration of dermal contact with the liquid product[c]
1. Manufacturing	Loading NMP into bulk containers	Data (2016 CDR[a])	Default Assumption	Activity-based Assumption
	Loading NMP into drums			

Exposure Scenario	Work Activity	NMP weight fraction in the liquid product	Total skin surface area of hands in contact with the liquid product[b]	Duration of dermal contact with the liquid product[c]
2. Repackaging	Unloading NMP from bulk containers	Data (2016 CDR[a])	Default Assumption	Activity-based Assumption
	Unloading NMP from drums			
3. Chemical Processing, Excluding Formulation	Unloading NMP from drums	Data (2016 CDR[a], public comments, and Use and Market Profile for N-Methylpyrrolidone[a])	Default Assumption	Activity-based Assumption
4. Incorporation into Formulation, Mixture, or Reaction Product	Unloading liquid NMP from drums	Data (2016 CDR[a], public comments, literature, and Use and Market Profile for N-Methylpyrrolidone[a])	Default Assumption	Activity-based Assumption
	Maintenance, bottling, shipping, loading			Default Assumption
5. Metal finishing	Spray application	Data (2012 and 2016 CDR[a])	Default Assumption	Default Assumption
	Dip application			
	Brush application			
6. Removal of Paints, Coatings, Adhesives and Sealants	Miscellaneous paint, coating, adhesive, and sealant removal	Data (public comments, literature, and Use and Market Profile for N-Methylpyrrolidone[a])	Default Assumption	Activity-based Assumption (central tendency) and Default Assumption (high-end)
	Graffiti removal			Default Assumption
7. Application of Paints, Coatings, Adhesives and Sealants	Spray application	Data (public comments, literature, and Use and Market Profile	Default Assumption	Default Assumption
	Roll/ curtain application			
	Dip application			

Exposure Scenario	Work Activity	NMP weight fraction in the liquid product	Total skin surface area of hands in contact with the liquid product[b]	Duration of dermal contact with the liquid product[c]
	Roller/ brush and syringe/ bead application	for N-Methylpyrrolidone[a])		
8. Electronic Parts Manufacturing	Container handling (small containers);	Data (SIA[a], public comments, literature, and Use and Market Profile for N-Methylpyrrolidone[a])	Default Assumption	Default Assumption
	Container handling, drums			
	Fab worker			
	Maintenance			
	Virgin NMP truck unloading			
	Waste truck loading			
9. Printing and Writing	Printing	Data (public comments, and Use and Market Profile for N-Methylpyrrolidone[a])	Default Assumption	Default Assumption
	Writing		Data (Australian Government Department of Health (2016))	Non-default Assumption
10. Soldering	Soldering	Data (Use and Market Profile for N-Methylpyrrolidone[a])	Default Assumption	Default Assumption
11. Commercial Automotive Servicing		Data (public comments and the Use and Market Profile for N-Methylpyrrolidone[a])	Default Assumption	Activity-based Assumption (central tendency) and Default Assumption (high-end)
12. Laboratory Use	Laboratory use	Non-default Assumption	Default Assumption	Activity-based Assumption

Exposure Scenario	Work Activity	NMP weight fraction in the liquid product	Total skin surface area of hands in contact with the liquid product[b]	Duration of dermal contact with the liquid product[c]
				(central tendency) and Default Assumption (high-end)
13. Cleaning	Dip cleaning / degreasing	Data (public comments, literature sources, and the Use and Market Profile for N-Methylpyrrolidone[a])	Default Assumption	Default Assumption
	Spray / wipe cleaning			
14. Fertilizer application	Spray application	Data (literature, public comments, and the Use and Market Profile for N-Methylpyrrolidone[a])	Default Assumption	Default Assumption
15. Wood preservatives	Brush application	Data (Use and Market Profile for N-Methylpyrrolidone[a])	Default Assumption	Default Assumption
16. Recycling and disposal	Unloading NMP from bulk containers	Data (SIA[a]) and Non-default Assumption	Default Assumption	Default Assumption
	Unloading NMP from drums			

a – Sources for weight fractions: 2016 CDR (U.S. EPA, 2017c), Use and Market Profile for N-Methylpyrrolidone (Abt, 2017), 2012 CDR (U.S. EPA, 2012b), SIA (2019), as well as various public comments and literature sources.
b – Default assumption for "Total skin surface area of hands in contact with the liquid product" is: (1) high-end value, which represents two full hands in contact with a liquid: 890 cm2 (mean for females),1070 cm2 (mean for males); (2) central tendency value, which is half of two full hands (equivalent to one full hand) in contact with a liquid and represents only the palm-side of both hands exposed to a liquid: 445 cm2 (females), 535 (males).
c – Default assumption for "Duration of dermal contact with the liquid product" is: (1) high-end value of a full-shift, usually 8 or 12 hours; central tendency value of value of half of a full-shift, usually 4 or 6 hours.

4.3.2 Data Uncertainties in Consumer Exposure Assessment

Systematic review was conducted to identify chemical- and product-specific monitoring and use data for assessing consumer exposures. As no product-specific monitoring data were identified, exposure

scenarios were assessed using a modeling approach that requires the input of various chemical parameters and exposure factors. When possible, default model input parameters were modified based on chemical and product specific inputs available in literature and product databases. Uncertainties related to these inputs are discussed below.

4.3.2.1 Product & Market Profile

The products and articles assessed in this risk evaluation are largely based on EPA's 2016-2017 Use and Market Profile for N-methyl-2-pyrrolidone, which provides information on commercial and consumer products available in the US marketplace at that time (Abt, 2017). While it is possible that some products may have changed since 2017, EPA believes that the timeframe is recent enough to still represent the current market. Information on products from the Use and Market Profile was augmented with other sources such as the NIH Household Product Survey and EPA's Chemical and Products Database (CPDat), as well as available product labels and safety data sheets (SDSs). However, it is still possible that the entire universe of products may not have been identified, due to market changes or research limitations.

4.3.2.2 Westat Survey

A number of product labels and/or technical fact sheets were identified for use in assessing consumer exposure. The identified information often did not contain product-specific use data, and/or represented only a small fraction of the product brands containing the chemical of interest. A comprehensive survey of consumer use patterns in the United States, called the Household Solvent Product: A National Usage Survey (U.S. EPA, 1987), was used to parameterize critical consumer modeling inputs, based on applicable product and use categories. This large survey of over 4,920 completed questionnaires, obtained through a randomized sampling technique, is highly relevant because the primary purpose was to provide statistics on the use of solvent-containing consumer products for the calculation of exposure estimates. The survey focused on 32 different common household product categories, generally associated with cleaning, painting, lubricating, and automotive care. Although there is uncertainty due to the age of the use pattern data, as specific products in the household product categories have likely changed over time, EPA assumes that the use pattern data presented in the Westat survey reflect reasonable estimates for current use patterns of similar product type. The Westat study aimed to answer the following key questions for each product category, some of which were used as key model inputs in this consumer assessment:

- room of product use (key input: environment of use),
- how much time was spent using the product (key input: duration of product use per event),
- how much of the product was used (key input: mass of product used per event),
- how often the products were used,
- when the product was last used,
- product formulation,
- brand names used, and
- degree of ventilation or other protective measures undertaken during product use.

The strengths and weakness of the Westat survey are discussed in more detail below with an emphasis on the key modeling inputs.

Product Use Category

A crosswalk was completed to assign consumer products in the current risk evaluation to one of the product or article scenarios in the CEM model, and then to an appropriate Westat survey category. Although detailed product descriptions were not provided in the Westat survey, a list of product brands

and formulation type in each category was useful in pairing the Westat product categories to the scenarios being assessed. In most cases, the product categories in the Westat survey aligned well with the products being evaluated. For product scenarios without an obvious Westat scenario match, professional judgment was used to make an assignment. For a limited number of scenarios, technical fact sheets or labels with information on product use amounts were available, and this information was used in the assessment as needed.

Another limitation of the Westat data is that while the overall respondent size of the survey was large, the number of users in each product category was varied, with some product categories having a much smaller pool of respondents than others. Product categories such as spot removers, cleaning fluids, glues and adhesives, lubricants, paints, wood stains, engine degreasers, and specialized electronic cleaners had sample sizes ranging from roughly 500 to 2,000 users; whereas, categories such as shoe polish, adhesive removers, rust removers, and brake cleaners had sample sizes of less than 500 users.

The survey was conducted for adults ages 18 and older. Most consumer products are targeted to this age category, and thus the respondent answers reflect the most representative age group. However, youth may also be direct users of some consumer products. It is unknown how the usage patterns compare between adult and youth users, but it is assumed that the product use patterns for adults will be very similar to, or more conservative (i.e., longer use duration, higher frequency of use) than use patterns for youth.

Room of Use

The CEM model requires specification of a room of use, which results in the following default model assumptions (relevant for inhalation exposure only): ventilation rates, room volume, and the amount of time per day that a person resides in the room of use. The Westat survey provided the location of product use for the following room categories: basement, living room, other inside room, garage, and outside. The room with the highest percentage was selected as the room to model in CEM. For some specific product scenarios, however, professional judgement was used to assign the room of use; these selections are documented above in Table 2-72 of Section 2.4.2.4. For many scenarios in which "other inside room" was the highest percentage, the utility room was selected as the default room of use. The utility room is a smaller room, and therefore may provide a more conservative assumption for peak concentrations. In cases where outside was identified as the "room of use," but it was deemed reasonable to assume the product could be used inside (such as for auto care products), the garage was typically selected as the room of use.

Amount of Product Used and Duration of Product Use

The Westat survey reported the number of ounces per use, derived from the fluid ounces of product used per year (based on can size and number of cans used), divided by the number of reported uses per year. The duration of use (in minutes) reported in Westat was a direct survey question. An advantage to these parameters is that the results are reported in percentile rankings and were used to develop profiles of high intensity, moderate intensity, and low intensity users of the products (95th, 50th, and 10th percentile values, respectively). In cases where a product was not crosswalked to a CEM scenario, the amount of product used was tailored to those specific products instead of depending on Westat data.

Ventilation and Protection

For most scenarios, the CEM model was run using median air exchange rates from EPA's Exposure Factors Handbook (2011), and interzone ventilation rates derived from the air exchange rates and the default median building volume from EPA's Exposure Factors Handbook (2011). These inputs do not incorporate any measures that would serve to increase air exchange. The Westat survey questions indicated that most respondents did not have an exhaust fan on when using these products, most respondents kept the door to the room open when using these products, and most people reported reading the directions on the label. The modeling conducted by EPA did not account for specific product instructions or warning labels. For example, some product labels might indicate that protective equipment (chemical resistant gloves or respirator) should be worn, which would lower estimated exposures

4.3.2.3 Other Parameters and Data Sources

Activity Patterns

EPA assumed that a consumer product would be used only once per day. This is a realistic assumption for most scenarios, but a high-intensity user could use the same product multiple times in one day. Additionally, CEM allows for selection of activity patterns based on a "stay-at-home" resident or a part-time or full-time "out-of-the home" resident. The activity patterns were developed based on Consolidated Human Activity Database (CHAD) data of activity patterns, which is an EPA database that includes more than 54,000 individual study days of detailed human behavior. It was assumed that the user followed a "stay-at-home" activity pattern that would place them in various rooms as well as outside of the home and room of use for more time than a part-time or full-time "out-of-the home" resident. Therefore, applying an "out-of-the home" resident activity pattern would reduce estimated exposures.

Product Density

If available, product-specific densities were obtained from SDS information, and used to convert the ounces of the product used from Westat, to grams of product used. If product-specific densities were not available, default product densities from the CEM User Guide were used.

Outdoor Scenario

The CEM model does not currently accommodate outdoor scenarios. For products that are solely intended to be used outdoors, modifications to the CEM inputs were made to simulate an outdoor scenario by adjusting Zone 1 parameters (which represents the room of use, or outside). The garage was selected as the room of use, but the room volume was changed to 16 m3 to represent a half dome chemical cloud around the person using the product. Additionally, the air exchange rate for Zone 1 was set to 100 to reflect the high rate between the cloud and the rest of outside. The interzone ventilation rate was set to 0, which effectively blocks the exchange of air between Zone 1 and the rest of the house. Thus, the concentrations users are exposed to inside the home after product use is zero. In the outside scenario, non-users are assumed to have zero exposures. These assumptions may be either an underestimate of exposures given outdoor conditions such as high temperatures in summer which could increase volatilization of NMP in the product but could also be an overestimate of exposures if outdoor conditions could include wind that effectively disperses the NMP in air.

4.3.3 Approach and Methodology for Uncertainties in Consumer Exposure Assessment

EPA's approach recognizes the need to include an uncertainty analysis. An important distinction for such an analysis concerns variability versus uncertainty – both aspects need to be addressed. Variability refers to the inherent heterogeneity or diversity of data in an assessment. It is "a quantitative description of the range or spread of a set of values" and is often expressed through statistical metrics, such as variance or standard deviation, that reflect the underlying variability of the data. Uncertainty refers to a lack of data or an incomplete understanding of the context of the risk assessment decision.

Variability cannot be reduced, but it can be better characterized. Uncertainty can be reduced by collecting more or better data. Quantitative methods to address uncertainty include non-probabilistic approaches such as sensitivity analysis and probabilistic methods such as Monte Carlo analysis. Uncertainty can also be addressed qualitatively, by including a discussion of factors such as data gaps and subjective decisions or instances where professional judgment was used.

4.3.3.1 Deterministic vs. Stochastic Approaches

With deterministic approaches, the output of the model is fully determined by the choices of parameter values and initial conditions. Stochastic approaches feature inherent randomness, such that a given set of parameter values and initial conditions can lead to an ensemble of different model outputs. Because EPA's largely deterministic approach involves choices regarding low, medium, and high values for highly influential factors such as chemical mass and frequency/duration of product use, it likely captures the range of potential exposure levels although it does not necessarily enable characterization of the full probabilistic distribution of all possible outcomes.

4.3.3.2 Sensitive Inputs

Certain inputs to which model outputs are sensitive, such as zone volumes and airflow rates, were not varied across product-use scenarios. As a result, model outcomes for extreme circumstances such as a relatively large chemical mass in a relatively low-volume environment likely are not represented among the model outcomes. Such extreme outcomes are believed to lie near the upper end (e.g., at or above the 90th percentile) of the exposure distribution.

4.3.4 Environmental Hazard and Exposure Assumptions Uncertainties

In the NMP Problem Formulation (U.S. EPA, 2018c) and this RE, EPA completed a screening level evaluation of environmental risk using inherently conservative assumptions. The analysis was completed using "high-end" estimated concentrations of NMP in the aquatic environment as described in Section 2.3.2 and compared those acute and chronic exposure estimates to conservative measures of acute and chronic hazard (concentrations of concern) as described in Section 3.1.2. EPA in the NMP Problem Formulation (U.S. EPA, 2018c) did not conduct any further analyses on pathways of exposure for terrestrial receptors as described in Section 2.5.3.1 of the NMP Problem Formulation and further described in Section 2.2 and 2.3 of this RE.

4.3.5 Human Health Hazard Assumptions and Uncertainties

There is a robust dataset for the critical reproductive and developmental effects that serve as the basis for the points of departure used in this risk characterization. High quality studies have consistently documented the developmental effects of NMP exposure across species and following dermal, oral, and

inhalation exposures. The high quality of studies, consistency of effects, relevance of effects for human health, coherence of the spectrum of reproductive and developmental effects observed and biological plausibility of the observed effects of NMP contribute to the overall confidence in the PODs identified based on reproductive and developmental endpoints.

Data on the reproductive and developmental toxicity of NMP in humans are not available. Therefore, this risk evaluation relies on the assumption that reproductive and developmental toxicity observed in animal models is relevant to human health. It is unknown whether this assumption contributes to an overestimate or underestimate of risk.

The rat PBPK model used to derive PODs based on internal doses facilitates integration of dose-response information from multiple high-quality studies that assessed the effects of NMP exposure across multiple routes. This model incorporates toxicokinetic information, reducing a key source of uncertainty in animal-to-human extrapolation. Furthermore, the availability of this model in combination with studies directly evaluating developmental toxicity across multiple exposure routes eliminates the need for route-to-route extrapolation thereby eliminating another source of uncertainty.

There are several remaining sources of uncertainty around the identification of PODs. As discussed in Section 3.2.1, there is uncertainty associated with the reproductive endpoints selected as the basis for the POD used to evaluate risks from chronic NMP exposure. Because NMP exposures occurred throughout development and into adulthood in the key study, it is not known which period(s) of exposure contributed to the reduced fertility seen in adult rats. It is also unclear which life stages may be most sensitive to the adverse reproductive effects of NMP exposure in humans. Although effects on male fertility and female fecundity were not consistently observed across studies, the POD derived from the key study is within close range of PODs derived from developmental endpoints that are consistently observed across studies, species, and routes of exposure. It is unknown whether the limited set of 2-generation studies contributed to an overestimate or underestimate of risk. The concordance of PODs across reproductive and developmental endpoints and consistency of developmental effects across species and exposure routes contributes to the overall confidence in the POD.

In developmental toxicity studies, there is inherent uncertainty around the potential contribution of maternal toxicity to observed developmental effects. The maternal effect reported in the Saillenfait (2003) inhalation study (transient decrease in body weight gain and food consumption) has been cited as a confounding factor by some study authors. EPA does not concur with this assertion, specifically as it relates to the observed decrease in maternal body weight gain on GD 6-21 (minus gravid uterine weight). Although a decrease in maternal body weight gain was observed, it is not statistically significant. Dams weighed roughly 235 g at GD 0, and whereas the controls gained approximately 32 grams, the high dose dams gained slightly less, roughly 26 grams. Given the lack of significant change in maternal body weight gain, it is unlikely that the observed decreases in fetal and pup body weights reflect a secondary effect of maternal toxicity. In other key and supporting studies, including an inhalation study (Solomon et al., 1995; E I Dupont De Nemours & Co, 1990), and an oral gavage study (Saillenfait et al., 2002), similar decreases in pup body weight were observed at similar exposure levels, in the absence of any effects on maternal body weight. These findings support EPA's conclusion that this developmental effect is a direct consequence of NMP exposure.

In addition, because the partial pressure of NMP depends on the temperature and relative humidity of the test system, variations in test protocol can introduce uncertainty regarding the actual exposure concentrations achieved in some of the inhalation studies used for hazard characterization. The PODs that were ultimately selected did not rely on studies with this source of uncertainty, making it unlikely that this uncertainty contributes to an overall over or under-estimate of risk.

Another important source of uncertainty around POD selection is the lack of complete information on potentially sensitive reproductive and developmental endpoints. Though the database for developmental toxicity is robust, some endpoints have not been fully characterized. For example, as described in Section 3.2.3.1, there is evidence of neurodevelopmental effects following gestational exposure to a relatively high dose of NMP, but a NOAEL for neurodevelopmental endpoints has not been identified. Incomplete information on potentially sensitive endpoints could lead to an underestimate of risk.

Overall, EPA has high confidence in the acute and chronic PODs identified for evaluating risk from NMP. The PODs are derived from endpoints that fall along a continuum of reproductive and developmental effects that are consistently observed in response to NMP across oral, dermal and inhalation exposure routes. Application of the PBPK model reduces uncertainties associated with extrapolation across species and exposure routes, further contributing to overall confidence in the PODs.

4.3.6 Risk Characterization Assumptions and Uncertainties

This risk characterization uses peer-reviewed human and rat PBPK models for NMP to make a direct comparison of internal doses (blood concentrations) predicted in humans in specific exposure scenarios to internal concentrations that occurred in rats in toxicology studies. The human PBPK models allows EPA to estimate total human exposures from combined inhalation and dermal exposures associated with specific exposure scenarios. The rat PBPK model facilitates integration of data from studies using different routes of exposure. Both models incorporate information on toxicokinetics, providing more robust exposure estimates and reducing uncertainties about species differences.

The peer-reviewed human PBPK models for NMP allow EPA to estimate total human exposures from combined inhalation and dermal exposures associated with specific exposure scenarios. The relative exposures from dermal, inhalation and vapor through skin can be deduced by comparing the internal exposure to workers due to inhalation, vapor through skin and dermal liquid contact with internal exposure to ONUs due to inhalation and vapor through skin exposure (a subtraction technique). The chronic exposures to workers assume no glove use and ONUs and calculated percent exposure due to dermal contact with liquid are shown in Table 4-50.

Table 4-49. Comparison of NMP Exposures by Route Showing Percent Exposure Due to Dermal Contact with Liquid from Chronic NMP Exposures [a]

Occupational Exposure Scenario [a]	Exposure Level [b]	Chronic Exposure Worker [c], AUC (hr mg/L) No gloves	Chronic Exposure ONU [d], AUC (hr mg/L)	Percent Exposure Due to Dermal Contact with Liquid [e]
Manufacturing of NMP	Central Tendency	8.6	0.011	100%

Occupational Exposure Scenario [a]	Exposure Level [b]	Chronic Exposure Worker [c], AUC (hr mg/L) No gloves	Chronic Exposure ONU [d], AUC (hr mg/L)	Percent Exposure Due to Dermal Contact with Liquid [e]
	High-End	81.4	0.31	100%
Repackaging	Central Tendency	8.6	0.011	100%
	High-End	81.4	0.31	100%
Chemical Processing, Excluding Formulation	Central Tendency	6.2	0.016	100%
	High-End	12.7	0.055	100%
Incorporation into Formulation, Mixture, or Reaction Product	Central Tendency	6.2	0.016	100%
	High-End	403.0	2.63	99%
Application of Paints, Coatings, Adhesives, and Sealants--Spray Application	Central Tendency	1.41	0.052	96%
	High-End	179.6	0.93	99%
Application of Paints, Coatings, Adhesives, and Sealants--Roll/curtain	Central Tendency	1.36	0.0059	100%
	High-End	178.4	0.052	100%
Application of Paints, Coatings, Adhesives, and Sealants--Dip	Central Tendency	1.55	0.19	88%
	High-End	179.1	0.57	100%
Application of Paints, Coatings, Adhesives, and Sealants--Brush	Central Tendency	2.18	0.81	63%
	High-End	179.5	0.85	100%
Printing	Central Tendency	3.4	0.0017	100%
	High-End	19.5	0.037	100%
Writing	Central Tendency	0.0016	0.000032	98%
	High-End	0.0032	0.00032	90%
Metal finishing - spray application	Central Tendency	44	0.053	100%
	High-End	347	0.94	100%
Metal finishing - dip	Central Tendency	44	0.20	100%
	High-End	346	0.58	100%
Metal finishing - brush	Central Tendency	45	0.81	98%
	High-End	347	0.86	100%
	Central Tendency	5.55	0.32	94%

Occupational Exposure Scenario [a]	Exposure Level [b]	Chronic Exposure Worker [c], AUC (hr mg/L) No gloves	Chronic Exposure ONU [d], AUC (hr mg/L)	Percent Exposure Due to Dermal Contact with Liquid[e]
Paint and coating removal - misc. removal	High-End	268	13	95%
Paint and coating removal - graffiti removal	Central Tendency	36.3	0.20	99%
	High-End	212	0.93	100%
Dip cleaning	Central Tendency	64.0	0.20	100%
	High-End	399	0.58	100%
Spray / Wipe Cleaning	Central Tendency	22.3	0.20	99%
	High-End	393	0.71	100%
Commercial Automotive Servicing	Central Tendency	0.92	0.49	47%
	High-End	113	8.91	92%
Laboratory Use	Central Tendency	36	0.010	100%
	High-End	400	0.81	100%
Electronic Parts Manufacturing--Electronics (Small Container Handling)	Central Tendency	67.4	0.15	100%
	High-End	444	0.21	100%
Electronic Parts Manufacturing--Electronics (Container Handling, Drums)	Central Tendency	55.1	0.0043	100%
	High-End	445	0.50	100%
Electronic Parts Manufacturing--Electronics (Fab worker)	Central Tendency	15.6	0.041	100%
	High-End	670	0.16	100%
Electronic Parts Manufacturing--Electronics (Maintenance)	Central Tendency	61.1	0.0064	100%
	High-End	671	0.25	100%
Electronic Parts Manufacturing--Electronics (Virgin NMP Truck Unloading)	Central Tendency	78.1	0.94	99%
	High-End	400	0.99	100%
Section 2.4.1.2.12 – Electronic Parts Manufacturing--Electronics (Waste Truck Unloading)	Central Tendency	70.22	0.14	100%
	High-End	356	0.17	100%
Soldering	Central Tendency	0.68	0.000025	100%
	High-End	6.8	0.00063	100%

Occupational Exposure Scenario [a]	Exposure Level [b]	Chronic Exposure Worker [c], AUC (hr mg/L) No gloves	Chronic Exposure ONU [d], AUC (hr mg/L)	Percent Exposure Due to Dermal Contact with Liquid [e]
Fertilizer Application	Central Tendency	0.66	0.58	11%
	High-End	20.6	1.1	95%
Wood preservative	Central Tendency	1.5	0.81	46%
	High-End	3.5	0.84	76%
Recycling and Disposal	Central Tendency	7.9	0.011	100%
	High-End	21.6	0.091	100%

[a] Use of PPE is not assumed for ONUs
Percent due to dermal liquid exposure is the worker exposure (inhalation, vapor through skin and dermal liquid contact) minus ONU exposure (inhalation and vapor through skin exposure) divided by worker exposure
[b] Central tendency means: typical air concentration for most scenarios. High-end means worst-case air concentration for most scenarios. ONUs are not expected to have direct contact with NMP-containing liquids (see Section 2.4.1.1). These exposure scenarios do not assume glove use.
[c] See tables of exposure estimates in Section 4.2.2
[d] See tables of exposure estimates in Section 4.2.3
[e] Due to rounding 100% is shown when the inhalation and vapor through skin exposures are small relative to dermal liquid contact however inhalation and vapor through skin exposures are not zero, see the exposure estimates and MOEs calculation in Section 4.2.3

Uncertainty factors used to generate benchmark MOEs used in the risk characterization account for various sources of uncertainty for each non-cancer POD. In this evaluation, benchmark MOEs for all scenarios are consistently low, reflecting the relatively low degree of overall uncertainty. As described in detail in Section 3.2.5.4, there are two uncertainty factors used in this risk characterization across all exposure scenarios:

- An interspecies uncertainty/variability factor of 3 (UF_A) was applied for animal-to-human extrapolation to account for toxicodynamic differences between species. Toxicokinetic differences are incorporated into PBPK models.
- A default intraspecies uncertainty/variability factor (UF_H) of 10 was applied to account for variation in sensitivity within human populations, including variation across gender, age, health status, or genetic makeup.

The human populations considered in this draft risk evaluation include pregnant women and men and women of reproductive age in occupational and consumer settings. Although exposures to younger non-users may be possible, there is insufficient data regarding specific genetic and/or life stage differences that could impact NMP metabolism and toxicity for further refinement of quantitative risk estimates. EPA does not have sufficient information to determine whether these uncertainty factors may lead to an overestimate or underestimate of risk.

4.4 Potentially Exposed or Susceptible Subpopulations

TSCA § 6(b)(4) requires that EPA conduct a risk evaluation to "*determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of cost or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation by the Administrator, under the conditions of use*." TSCA § 3(12) states that "*the term 'potentially exposed or susceptible subpopulation' means a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly*."

As described in Section 3.2.5.2, certain biological characteristics may increase susceptibility to NMP exposure. The developmental effects identified as a critical human health endpoint for acute exposures in this draft risk evaluation are a major concern for pregnant women, the developing fetus, and women who may become pregnant. The reproductive effects identified as a critical human health endpoint for chronic exposures may be of concern for all adults of reproductive age as well as for children and adolescents whose reproductive systems are still developing. Other populations that may be more sensitive to the hazards of NMP exposure include people with pre-existing conditions, and people with lower metabolic capacity due to life stage, genetic variation, or impaired liver function. The magnitude of the effect of each of these factors alone or in combination on overall risk is unknown.

The acute and chronic PODs used in this risk characterization are based on studies that evaluated effects of exposure during sensitive life stages in rats. Toxicology data (Exxon, 1991) demonstrate early postnatal body weight decreases and early postnatal death at doses that are greater than the POD derived for decreased fertility from the same study. It is considered likely that these postnatal outcomes are the result of repeated exposures to NMP. These findings could be considered a surrogate for analysis of risks to newborns and young infants.

There is insufficient information to support a quantitative analysis of interindividual variability in other potentially susceptible populations. An uncertainty factor of 10 was applied to account for uncertainty related to interindividual variability, but the actual effect of various factors contributing to biological susceptibility on overall risk is unknown.

As described in Section 2.5.1, EPA identified workers, occupational non-users, consumers of NMP-containing products and bystanders, including children, as potentially exposed populations. The exposure factors and hazard endpoints used in this draft risk evaluation are representative of the most sensitive subpopulations (i.e., pregnant women or women who might become pregnant, male workers, and the fetus). The associated risk findings are expected to be protective of children and adolescents. In developing the risk evaluation, the EPA analyzed the reasonably available information to ascertain whether some human receptor groups may have greater exposure than the general population to the hazard posed by a chemical. For example, EPA estimated acute exposures for children who may be located near the consumer user at the time of use and determined that these exposures were below levels that may pose a risk.

4.5 Aggregate and Sentinel Exposures

Section 2605(b)(4)(F)(ii) of TSCA requires the EPA, as a part of the risk evaluation, to describe whether aggregate or sentinel exposures under the conditions of use were considered and the basis for their consideration. The EPA has defined aggregate exposure as "*the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways* (40 CFR § 702.33)."

In many exposure scenarios, NMP exposure occurs through multiple routes. Considering risk from a single exposure route at a time instead of evaluating total exposures could underestimate risk. This risk characterization therefore relies on exposure estimates that account for multiple simultaneous routes of exposure to NMP. Exposure for each condition of use was evaluated by determining both the exposure to NMP vapor and dermal contact with the liquid. Time profiles of each type of exposure were estimated for a variety of job categories and household consumer uses, behaviors, and activity profiles. Vapor exposure is specified by the air concentration encountered as a function of time during the work-day or for 24 h from the start of a household application. Dermal contact is characterized by the weight fraction (WF) of NMP in the product being used, the surface area of skin (hands) exposed, and the duration of the dermal exposure. For workplace exposures vapor and dermal exposures are assumed to be only simultaneous (both end at the end of the task, shift, or work day). For household exposures vapor exposure typically continues for some time after the application is complete due to slower air exchange but is lower for the rest of house than the location where the project is done, with movement of the individual between these zones included. Dermal exposure for consumers is also limited to the user's direct contact with the product as defined by the duration of use.

The PBPK exposure model was used to integrate absorption from both vapor and liquid contact via three pathways: inhalation of vapors, absorption of liquid in contact with the skin, and absorption of vapor by exposed skin. Exhalation and desorption of vapor from skin are also post-exposure elimination pathways. Vapor absorption through the skin is a minor component of total exposure in most scenarios but is included for completeness and uses the same dermal resistance as liquid absorption to account for absorption from un-occluded areas of the face, neck, arms and hands. Use of a face mask is assumed to reduce concentration inside the mask by a factor of 10 (i.e., the mask has a protection factor, PF = 10) while use of gloves is assumed to reduce the surface area of the skin exposed to liquid NMP, where the PF was varied for different quality gloves.

While this assessment evaluates specific COUs based on exposure estimates that incorporate multiple routes of exposure, it does not consider the potential for aggregate exposures from multiple conditions of use. For example, it does not evaluate the aggregate risk to individuals exposed via occupational and consumer uses. This could result in an underestimate of risk.

EPA defines sentinel exposure as "*the exposure to a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures* (40 CFR § 702.33)." In this risk evaluation, EPA considered sentinel exposure in the form of high-end estimates for consumer and occupational exposure scenarios which incorporate dermal and inhalation exposure, as these routes are expected to present the highest exposure potential based on details provided for the manufacturing, processing and use scenarios discussed in Section 2.4. The

exposure calculation used to estimate dermal exposure to liquid is conservative for high-end occupational and consumer scenarios where it assumes full contact of both hands and no glove use.

4.6 Risk Conclusions

4.6.1 Environmental Risk Conclusions

No risks to fish, aquatic invertebrates or algae were identified from NMP releases to ambient water. EPA used environmental release data from EPA's Toxics Release Inventory (TRI) and a "first-tier" exposure assessment to derive conservative estimates of NMP surface water concentrations near facilities reporting the highest NMP water releases. Using the 2015 TRI data and EPA's Exposure and Fate Assessment Screening Tool (EFAST, Version 2014) EPA predicted NMP surface water concentrations as high as 224 µg/L and 1,496 µg/L for the acute and chronic exposure scenarios, respectively. Based on this analysis the acute and chronic RQs are 0.0022 and 0.85, respectively indicating a low concern for risks to aquatic organisms from NMP exposures via surface water.

4.6.2 Human Health Risk Conclusions

In general, the conditions of use that present the lowest concern for human health risks include those that incorporate a high level of containment or small-scale use of NMP. The conditions of use which involve a lower level of containment, elevated temperatures or high intensity use show greater risk even when personal protective equipment is considered. For example, high-end occupational exposure estimates for NMP use in cleaning, metal finishing, electronic parts manufacturing, automotive servicing, and use in (or removal of) paints, coatings, adhesives and sealants show risks that are not mitigated via glove use.

For consumers, risk concerns are indicated for acute exposures associated with high-intensity use of paint removers, degreasers and engine degreasers (see Table 4-51). The main factors that impact consumer exposures during use of NMP-containing products include the NMP weight fraction, duration of product use and the actual amount of product used (see Table 2-79 and Table 2-85). In addition, specific factors related to the room of use (e.g., room size, air exchange rate) may affect the estimated NMP air concentrations to which consumers may be exposed. For example, air concentrations can vary depending on whether windows or garage doors are open or closed during product use. Variations in individual activity patterns can also impact exposure potential (e.g., risks associated with the engine degreasing activity may be underestimated if the product is used continuously). Bystander exposures were estimated for conditions of use that presented risks to the product user; these exposure scenarios did not present a risk concern to bystanders located outside the room of product use.

EPA has high confidence in the hazard endpoints used to evaluate risks associated with acute and chronic NMP exposure. As discussed in Section 3.2.6, fetal resorptions (mortality) and reduced fertility were considered relevant hazards for evaluating risks following acute and chronic NMP exposure, respectively. While there is some uncertainty regarding temporal windows of vulnerability for developmental toxicity and whether the timing of a single exposure can produce a permanent adverse effect on human development, EPA considers the developmental toxicity endpoints associated with NMP exposure to be applicable to acute exposures. The available literature suggests that a single developmental exposure may have sustained effects on the conceptus. Fetal mortality represents the most severe endpoint associated with the developmental hazard profile for NMP. Reduced fertility in

6678 males is the most sensitive effect associated with chronic exposures. The chronic POD based on effects
6679 on reduced male fertility is supported by effects on female fecundity and developmental toxicity in a
6680 similar dose range.
6681

6682 **Table 4-50. Summary of Risk Estimates for Aggregate Exposures to Workers by Condition of Use**

Life Cycle Stage/ Category	Subcategory	Occupational Exposure Scenario	Population	Exposure Level	Risk Estimates for No PPE		Risk Estimates with PPE	
					Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)	Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)
Manufacture/Domestic manufacture	Domestic Manufacture	Section 2.4.1.2.1 – Manufacturing	Worker	Central Tendency	52	**21**	1025 (PF 20)	423 (PF 20)
				High-End	**9.9**	**2.2**	194 (PF 20)	48 (PF 20)
			ONU	Central Tendency	–	16,344	N/A	N/A
				High-End	–	587	N/A	N/A
Manufacture/Import	Import	Section 2.4.1.2.2 – Repackaging	Worker	Central Tendency	52	**21**	518 (PF 10)	213 (PF 10)
				High-End	**9.9**	**2.2**	101 (PF 10)	**25 (PF 10)**
			ONU	Central Tendency	–	16,344	N/A	N/A
				High-End	–	587	N/A	N/A
Processing/Processing as a reactant or intermediate	Intermediate in plastic material and resin and pharmaceutical and medicine manufacturing	Section 2.4.1.2.3 – Chemical Processing, Excluding Formulation	Worker	Central Tendency	62	**29**	612 (PF 10)	291 (PF 10)
	Other			High-End	31	**14**	301(PF 10)	143 (PF 10)
			ONU	Central Tendency	–	11,255	N/A	N/A
				High-End	–	3,343	N/A	N/A
Processing/Incorporated into formulation, mixture or reaction product	Adhesives and sealant chemicals in Adhesive Manufacturing	Section 2.4.1.2.4 – Incorporation into Formulation, Mixture, or Reaction Product	Worker	Central Tendency	62	**29**	612 (PF10)	291(PF 10)
	Anti-adhesive agents in Printing and Related Support Activities			High-End	**4.1**	**0.5**	49 (PF 10)	**6 (PF 10)**
	Paint additives and coating additives not described by other codes in Paint and Coating Manufacturing; and Print Ink Manufacturing		ONU	Central Tendency	–	11,255	N/A	N/A
				High-End	–	70	N/A	N/A
	Processing aids not otherwise listed in Plastic Material and Resin Manufacturing							

Life Cycle Stage/ Category	Subcategory	Occupational Exposure Scenario	Population	Exposure Level	Risk Estimates for No PPE		Risk Estimates with PPE	
					Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)	Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)
	Manufacturing; Primary Metal Manufacturing; Soap, Cleaning Compound and Toilet Preparation Manufacturing; Transportation Equipment Manufacturing; All Other Chemical Preparation Manufacturing; Printing and Related Support Activities; Services; Wholesale and Retail Trade Product and							
	Surface active agents in Soap, Cleaning Compound and Toilet Preparation Manufacturing							
	Plating agents and surface treating agents in Fabricated Metal Product Manufacturing							
	Solvents (which become part of product formulation or mixture) in Electrical Equipment, Appliance and Component Manufacturing; Other Manufacturing; Paint and Coating Manufacturing; Print Ink Manufacturing; Soap, Cleaning Compound and Toilet Preparation Manufacturing; Transportation Equipment Manufacturing; All Other Chemical Product and Preparation Manufacturing; Printing and Related Support Activities; Wholesale and Retail Trade							
	Other uses in Oil and Gas Drilling, Extraction and Support Activities; Plastic Material and Resin Manufacturing; Services							
Processing/Incorporated into article	Lubricants and lubricant additives in Machinery Manufacturing	Section 2.4.1.2.5 – Metal Finishing (Spray Application)	Worker	Central Tendency	**23**	**4.2**	235 (PF 10)	44 (PF 10)
				High-End	**4.7**	**0.5**	58 (PF 10)	**7 (PF 10)**
			ONU	Central Tendency	–	3,428	N/A	N/A
				High-End	–	195	N/A	N/A

Life Cycle Stage/ Category	Subcategory	Occupational Exposure Scenario	Population	Exposure Level	Risk Estimates for No PPE		Risk Estimates with PPE	
					Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)	Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)
	Paint additives and coating additives not described by other codes in Transportation Equipment Manufacturing	Section 2.4.1.2.7 – Application of Paints, Coatings, Adhesives, and Sealants (Spray Application)	Worker	Central Tendency	690	130	5152 (PF 10)	976 (PF 10)
				High-End	**8.7**	**1.0**	97 (PF 10)	**12 (PF 10)**
			ONU	Central Tendency	–	3,525	N/A	N/A
				High-End	–	197	N/A	N/A
		Section 2.4.1.2.7 – Application of Paints, Coatings, Adhesives, and Sealants (Roll/Curtain)	Worker	Central Tendency	714	134	6880 (PF 10)	1294 (PF 10)
				High-End	**8.8**	**1.0**	103 (PF10)	**12 (PF 10)**
			ONU	Central Tendency	–	30,904	N/A	N/A
				High-End	–	3,522	N/A	N/A
		Section 2.4.1.2.7 – Application of Paints, Coatings, Adhesives, and Sealants (Dip)	Worker	Central Tendency	623	118	2,092 (PF 10)	556 (PF 10)
				High-End	**8.8**	**1.0**	99 (PF 10)	**12 (PF 10)**
			ONU	Central Tendency	–	944	N/A	N/A
				High-End	–	321	N/A	N/A
		Section 2.4.1.2.7 – Application of Paints, Coatings, Adhesives, and Sealants (Brush)	Worker	Central Tendency	440	84	1003 (PF 10)	194 (PF 10)
				High-End	**8.7**	**1.0**	97 (PF 10)	**12 (PF 10)**
			ONU	Central Tendency	–	226	N/A	N/A
				High-End	–	215	N/A	N/A
	Solvents (which become part of product formulation or mixture), including in Textiles, Apparel and Leather Manufacturing	Section 2.4.1.2.4 – Incorporation into Formulation, Mixture, or Reaction Product	Worker	Central Tendency	62	**29**	612 (PF 10)	291 (PF 10)
				High-End	**4.1**	**0.5**	49 (PF 10)	**6 (PF 10)**
			ONU	Central Tendency	–	11,255	N/A	N/A

Life Cycle Stage/ Category	Subcategory	Occupational Exposure Scenario	Population	Exposure Level	Risk Estimates for No PPE		Risk Estimates with PPE	
					Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)	Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)
				High-End	–	70	N/A	N/A
	Other, including in Plastic Product Manufacturing	Section 2.4.1.2.3 – Chemical Processing, Excluding Formulation	Worker	Central Tendency	62	**29**	612 (PF 10)	291 (PF 10)
				High-End	31	**14**	301 (PF 10)	143(PF 10)
			ONU	Central Tendency	–	11,255	N/A	N/A
				High-End	–	3,343	N/A	N/A
Processing/Recycling	Recycling	Section 2.4.1.2.16 – Recycling and Disposal	Worker	Central Tendency	56	**23**	282 (PF 5)	116 (PF 5)
				High-End	**23**	**8.5**	114 (PF 5)	43 (PF 5)
			ONU	Central Tendency	–	16,530	N/A	N/A
				High-End	–	2,007	N/A	N/A
Processing/Repackaging	Wholesale and Retail Trade	Section 2.4.1.2.2 – Repackaging	Worker	Central Tendency	52	**21**	518(PF 10)	213 (PF 10)
				High-End	**9.9**	**2.2**	101 (PF 10)	**25 (PF 10)**
			ONU	Central Tendency	–	16,344	N/A	N/A
				High-End	–	587	N/A	N/A
Distribution in Commerce/ Distribution	Distribution in commerce	Distribution in commerce	Worker	Central Tendency	**Not separately addressed**			
Industrial, commercial, and consumer use/Paint and coatings	Paint and coating removers	Section 2.4.1.2.6 - Removal of Paints, Coatings, Adhesives, and Sealants (Misc. Removal)	Worker	Central Tendency	104	33	687 (PF 10)	218 (PF 10)
	Adhesive removers			High-End	**5.9**	**0.7**	46 (PF 10)	**6 (PF 10)**
			ONU	Central Tendency	–	566	N/A	N/A
				High-End	–	**14**	N/A	N/A
		Section 2.4.1.2.6 - Removal of Paints,	Worker	Central Tendency	**27**	**5.0**	270 (PF 10)	51 (PF 10)

Life Cycle Stage/ Category	Subcategory	Occupational Exposure Scenario	Population	Exposure Level	Risk Estimates for No PPE		Risk Estimates with PPE	
					Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)	Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)
		Coatings, Adhesives, and Sealants (Graffiti Removal)		High-End	**7.4**	**0.9**	85 (PF 10)	**10 (PF 10)**
			ONU	Central Tendency	–	920	N/A	N/A
				High-End	–	196	N/A	N/A
	Lacquers, stains, varnishes, primers and floor finishes	Section 2.4.1.2.7 – Application of Paints, Coatings, Adhesives, and Sealants (Spray Application)	Worker	Central Tendency	690	130	5152 (PF 10)	976 (PF10)
	Powder coatings (surface preparation)			High-End	**8.7**	**1.0**	97 (PF 10)	**12 (PF 10)**
			ONU	Central Tendency	–	3,525	N/A	N/A
				High-End	–	197	N/A	N/A
Industrial, commercial, and consumer use/Paint additives and coating additives not described by other codes	Use in Computer and Electronic Product Manufacturing, Construction, Fabricated Metal Product Manufacturing, Machinery Manufacturing, Other Manufacturing, Paint and Coating Manufacturing, Primary Metal Manufacturing, Transportation Equipment Manufacturing, Wholesale and Retail Trade	Section 2.4.1.2.7 – Application of Paints, Coatings, Adhesives, and Sealants (Roll/Curtain)	Worker	Central Tendency	714	134	6880 (PF 10)	1294 (PF 10)
				High-End	**8.8**	**1.0**	103 (PF 10)	**12 (PF 10)**
			ONU	Central Tendency	–	30,904	N/A	N/A
				High-End	–	3,522	N/A	N/A
Industrial, commercial, and consumer use/Adhesives and sealants	Adhesives and sealant chemicals including binding agents	Section 2.4.1.2.7 – Application of Paints, Coatings, Adhesives, and Sealants (Dip)	Worker	Central Tendency	623	118	2,092 (PF 10)	556 (PF10)
	Single component glues and adhesives, including lubricant adhesives			High-End	**8.8**	**1.0**	99 (PF 10)	**12 (PF 10)**
	Two-component glues and adhesives, including some resins		ONU	Central Tendency	–	944	N/A	N/A
				High-End	–	321	N/A	N/A
	Two-component glues and adhesives, including some resins	Section 2.4.1.2.7 – Application of Paints, Coatings, Adhesives, and Sealants (Brush)	Worker	Central Tendency	440	84	1003 (PF 10)	194 (PF 10)
				High-End	**8.7**	**1.0**	97 (PF 10)	**12 (PF 10)**
			ONU	Central Tendency	–	226	N/A	N/A
				High-End	–	215	N/A	N/A

Life Cycle Stage/ Category	Subcategory	Occupational Exposure Scenario	Population	Exposure Level	Risk Estimates for No PPE		Risk Estimates with PPE	
					Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)	Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)
Industrial, commercial, and consumer use/Solvents (for cleaning or degreasing)	Use in Electrical Equipment, Appliance and Component Manufacturing	Section 2.4.1.2.8 – Electronic Parts Manufacturing: Electronics (Container Handling, Small Containers)	Worker	Central Tendency	**19**	**2.7**	204 (PF 10)	29 (PF 10)
				High-End	**4.7**	**0.4**	65 (PF 10)	**6(PF 10)**
			ONU	Central Tendency	–	1,225	N/A	N/A
				High-End	–	859	N/A	N/A
Industrial, commercial, and consumer use/Ink, toner, and colorant products	Printer Ink	Section 2.4.1.2.9 - Printing and Writing: Printing	Worker	Central Tendency	286	54	1,433 (PF 5)	269 (PF 5)
				High-End	78	**9.4**	395 (PF 5)	48 (PF 5)
			ONU	Central Tendency	–	108,142	N/A	N/A
				High-End	–	5,001	N/A	N/A
	Inks in writing	Section 2.4.1.2.9 - Printing and Writing: Writing	Worker	Central Tendency	232,401	115,998	1,165,010 (PF 5)	578,327 (PF 5)
				High-End	116,201	57,998	582,823 (PF 5)	289,149 (PF 5)
			ONU	Central Tendency	–	5,784,391	N/A	N/A
				High-End	–	580,007	N/A	N/A
Industrial, commercial, and consumer use/Processing aids, specific to petroleum production	Petrochemical Manufacturing	Section 2.4.1.2.3 - Chemical Processing, Excluding Formulation	Worker	Central Tendency	62	**29**	612 (PF 10)	291(PF 10)
				High-End	31	**14**	301 (PF 10)	143 (PF 10)
			ONU	Central Tendency	–	11,255	N/A	N/A
				High-End	–	3,343	N/A	N/A
Industrial, commercial, and consumer use/Other uses	Other uses in Oil and Gas Drilling, Extraction and Support Activities	Section 2.4.1.2.3 - Chemical Processing, Excluding Formulation	Worker	Central Tendency	62	**29**	612 (PF 10)	291 (PF 10)
	Pharmaceutical and Medicine Manufacturing – functional fluids (closed systems)			High-End	31	**14**	301 (PF 10)	143(PF 10)
			ONU	Central Tendency	–	11,255	N/A	N/A

Life Cycle Stage/ Category	Subcategory	Occupational Exposure Scenario	Population	Exposure Level	Risk Estimates for No PPE		Risk Estimates with PPE	
					Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)	Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)
				High-End	–	3,343	N/A	N/A
	Lithium ion batteries	Section 2.4.1.2.8 – Electronic Parts Manufacturing: Electronics (Container Handling, Drums)	Worker	Central Tendency	**24**	**3.3**	251 (PF 10)	36 (PF 10)
				High-End	**4.7**	**0.4**	64(PF 10)	**6 (PF 10)**
			ONU	Central Tendency	–	42,649	N/A	N/A
				High-End	–	368	N/A	N/A
		Section 2.4.1.2.8 – Electronic Parts Manufacturing: Electronics (Fab Worker)	Worker	Central Tendency	82	**12**	820 (PF10)	117 (PF 10)
				High-End	**3.2**	**0.3**	48 (PF 10)	**4 (PF 10)**
			ONU	Central Tendency	–	4,502	N/A	N/A
				High-End	–	1,137	N/A	N/A
		Section 2.4.1.2.8 – Electronic Parts Manufacturing: Electronics (Maintenance)	Worker	Central Tendency	**21**	**3.0**	228 (PF 10)	32 (PF 10)
				High-End	**3.2**	**0.3**	48 (PF 10)	**4 (PF 10)**
			ONU	Central Tendency	–	28,624	N/A	N/A
				High-End	–	739	N/A	N/A
		Section 2.4.1.2.8 – Electronic Parts Manufacturing: Electronics (Virgin NMP Truck Unloading)	Worker	Central Tendency	**13**	**2.3**	125 (PF 10)	23 (PF 10)
				High-End	**4.1**	**0.5**	52 (PF 10)	**6 (PF 10)**
			ONU	Central Tendency	–	195	N/A	N/A
				High-End	–	184	N/A	N/A
		Section 2.4.1.2.8 – Electronic Parts Manufacturing: Electronics	Worker	Central Tendency	**14**	**2.6**	151 (PF 10)	28 (PF 10)
				High-End	**4.6**	**0.5**	59 (PF 10)	**7 (PF 10)**

Life Cycle Stage/ Category	Subcategory	Occupational Exposure Scenario	Population	Exposure Level	Risk Estimates for No PPE		Risk Estimates with PPE	
					Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)	Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)
		(Waste Truck Unloading)	ONU	Central Tendency	–	1,313	N/A	N/A
				High-End	–	1,097	N/A	N/A
	Soldering materials	Section 2.4.1.2.10 - Soldering	Worker	Central Tendency	1,436	270	14376(PF 10)	2701 (PF 10)
				High-End	222	**27**	2242(PF 10)	270 (PF 10)
			ONU	Central Tendency	–	7,224,526	N/A	N/A
				High-End	–	289,802	N/A	N/A
	Anti-freeze and de-icing products	Section 2.4.1.2.11 - Commercial Automotive Servicing	Worker	Central Tendency	624	199	1,090 (PF 10)	344 (PF 10)
	Automotive care products							
	Lubricants and greases			High-End	**14**	**1.6**	84 (PF10)	**10 (PF 10)**
			ONU	Central Tendency	–	374	N/A	N/A
				High-End	–	**21**	N/A	N/A
	Metal products not covered elsewhere	Section 2.4.1.2.5 – Metal Finishing (Spray Application)	Worker	Central Tendency	**23**	**4.2**	235 (PF 10)	44 (PF 10)
				High-End	**4.7**	**0.5**	58 (PF 10)	**7 (PF 10)**
			ONU	Central Tendency	–	3,428	N/A	N/A
				High-End	–	195	N/A	N/A
		Section 2.4.1.2.5 – Metal Finishing (Dip)	Worker	Central Tendency	**23**	**4.2**	227 (PF 10)	43 (PF 10)
				High-End	**4.7**	**0.5**	59 (PF 10)	**7 (PF 10)**
			ONU	Central Tendency	–	937	N/A	N/A
				High-End	–	316	N/A	N/A
			Worker	Central Tendency	**22**	**4.1**	198 (PF 10)	37 (PF 10)

Life Cycle Stage/ Category	Subcategory	Occupational Exposure Scenario	Population	Exposure Level	Risk Estimates for No PPE		Risk Estimates with PPE	
					Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)	Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)
		Section 2.4.1.2.5 – Metal Finishing (Brush)		High-End	**4.7**	**0.5**	58 (PF 10)	**7 (PF 10)**
			ONU	Central Tendency	–	226	N/A	N/A
				High-End	–	213	N/A	N/A
	Lubricant and lubricant additives, including hydrophilic coatings	Section 2.4.1.2.5 – Metal Finishing (Spray Application)	Worker	Central Tendency	**23**	**4.2**	235 (PF 10)	44 (PF 10)
				High-End	**4.7**	**0.5**	58 (PF 10)	**7 (PF 10)**
			ONU	Central Tendency	–	3,428	N/A	N/A
				High-End	–	195	N/A	N/A
		Section 2.4.1.2.5 – Metal Finishing (Dip)	Worker	Central Tendency	**23**	**4.2**	227 (PF 10)	43 (PF 10)
				High-End	**4.7**	**0.5**	59 (PF 10)	**7 (PF 10)**
			ONU	Central Tendency	–	937	N/A	N/A
				High-End	–	316	N/A	N/A
		Section 2.4.1.2.5 – Metal Finishing (Brush)	Worker	Central Tendency	**22**	**4.1**	198 (PF 10)	37 (PF 10)
				High-End	**4.7**	**0.5**	58 (PF 10)	**7 (PF 10)**
			ONU	Central Tendency	–	226	N/A	N/A
				High-End	–	213	N/A	N/A
	Laboratory chemicals	Section 2.4.1.2.12 - Laboratory Use	Worker	Central Tendency	**21**	**5.0**	214 (PF 10)	53 (PF 10)
				High-End	**4.1**	**0.5**	52 (PF 10)	**6 (PF 10)**
			ONU	Central Tendency	–	17,565	N/A	N/A
				High-End	–	225	N/A	N/A

Life Cycle Stage/ Category	Subcategory	Occupational Exposure Scenario	Population	Exposure Level	Risk Estimates for No PPE		Risk Estimates with PPE	
					Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)	Acute Non-cancer (benchmark MOE = 30)	Chronic Non-cancer (benchmark MOE = 30)
	Cleaning and furniture care products, including wood cleaners, gasket removers	Section 2.4.1.2.13 – Cleaning (Dip Cleaning)	Worker	Central Tendency	**16**	**2.9**	163 (PF 10)	31 (PF 10)
				High-End	**4.1**	**0.5**	53 (PF 10)	**6 (PF 10)**
			ONU	Central Tendency	–	934	N/A	N/A
				High-End	–	314	N/A	N/A
		Section 2.4.1.2.13 – Cleaning (Spray/Wipe Cleaning)	Worker	Central Tendency	44	**8.2**	418 (PF 10)	79 (PF 10)
				High-End	**4.2**	**0.5**	53 (PF 10)	**6 (PF 10)**
			ONU	Central Tendency	–	922	N/A	N/A
				High-End	–	258	N/A	N/A
	Fertilizer and other agricultural chemical manufacturing-processing aids and solvents	Section 2.4.1.2.14 - Fertilizer Application	Worker	Central Tendency	1,430	279	1,587 (PF 5)	307 (PF 5)
				High-End	74	**8.9**	310 (PF 5)	38 (PF 5)
			ONU	Central Tendency	–	315	N/A	N/A
				High-End	–	171	N/A	N/A
	Wood preservatives	Section 2.4.1.2.15 - Wood Preservatives	Worker	Central Tendency	635	122	1,003 (PF 5)	194 (PF 5)
				High-End	426	52	1,099 (PF 5)	135 (PF 5)
			ONU	Central Tendency	–	226	N/A	N/A
				High-End	–	219	N/A	N/A

N/A = not assessed because ONUs are not assumed to be wearing PPE; - = exposure data for ONUs were not available

6689 **Table 4-51. Summary of Risk Estimates from Acute Exposures to Consumers by Conditions of Use**

Life Cycle Stage/ Category	Subcategory	Consumer Condition of Use/Exposure Scenario	Population	Exposure Level	Risk Estimate
					Acute Non-cancer (benchmark MOE = 30)
Industrial, commercial, and consumer use/ Paints and coatings	Paint and coating removers	Section 2.4.2.5, Paint Removers	Consumer	Medium-Intensity User	107
				High-Intensity User	**22**
			Bystander	Medium-Intensity User	N/A
				High-Intensity User	N/A
	Adhesive removers	Section 2.4.2.5, Adhesive Removers	Consumer	Medium-Intensity User	167
				High-Intensity User	36
			Bystander	Medium-Intensity User	N/A
				High-Intensity User	N/A
	Lacquer, stains, varnishes, primers and floor finishes	Section 2.4.2.5, Stains, Varnishes	Consumer	Medium-Intensity User	633
				High-Intensity User	111
			Bystander	Medium-Intensity User	N/A
				High-Intensity User	N/A
Industrial, commercial, and consumer use/ Paint additives and coatings additives not described by other codes	Use in Computer and Electronic Product Manufacturing, Construction, Fabricated Metal Product Manufacturing, Machinery Manufacturing, Other Manufacturing, Paint and Coating Manufacturing, Primary Metal Manufacturing, Transportation Equipment Manufacturing, Wholesale and Retail Trade	Section 2.4.2.5, Paint	Consumer	Medium-Intensity User	578
				High-Intensity User	152
			Bystander	Medium-Intensity User	N/A
				High-Intensity User	N/A
		Section 2.4.2.5, Arts and Crafts	Consumer	Medium-Intensity User	3,034
				High-Intensity User	974
			Bystander	Medium-Intensity User	N/A
				High-Intensity User	N/A
Industrial, commercial, and		Section 2.4.2.5, Adhesives	Consumer	Medium-Intensity User	174
				High-Intensity User	38

Life Cycle Stage/ Category	Subcategory	Consumer Condition of Use/Exposure Scenario	Population	Exposure Level	Risk Estimate
					Acute Non-cancer (benchmark MOE = 30)
consumer use/ adhesives and sealants	Single component glues and adhesives, including lubricant adhesives		Bystander	Medium-Intensity User	N/A
				High-Intensity User	N/A
	Two-component glues and adhesives, including some resins	Section 2.4.2.5, Sealants	Consumer	Medium-Intensity User	19,115
				High-Intensity User	3,086
			Bystander	Medium-Intensity User	N/A
				High-Intensity User	N/A
Industrial, commercial, and consumer use/ Other uses	Automotive care products	Section 2.4.2.5, Auto Interior Cleaner	Consumer	Medium-Intensity User	844
				High-Intensity User	50
			Bystander	Medium-Intensity User	N/A
				High-Intensity User	N/A
		Section 2.4.2.5, Auto Interior Spray Cleaner	Consumer	Medium-Intensity User	2,323
				High-Intensity User	1,180
			Bystander	Medium-Intensity User	N/A
				High-Intensity User	N/A
	Cleaning and furniture care products, including wood cleaners, gasket removers	Section 2.4.2.5, Cleaners/Degreaser	Consumer	Medium-Intensity User	209
				High-Intensity User	**16**
			Bystander	Medium-Intensity User	N/A
				High-Intensity User	53
		Section 2.4.2.5, Engine Cleaner/ Degreaser	Consumer	Medium-Intensity User	128
				High-Intensity User	**13**
			Bystander	Medium-Intensity User	N/A
				High-Intensity User	39
		Section 2.4.2.5,	Consumer	Medium-Intensity User	651

Life Cycle Stage/ Category	Subcategory	Consumer Condition of Use/Exposure Scenario	Population	Exposure Level	Risk Estimate
					Acute Non-cancer (benchmark MOE = 30)
Industrial, commercial, and consumer use/ Other uses	Lubricant and lubricant additives, including hydrophilic coatings	Spray Lubricant		High-Intensity User	76
			Bystander	Medium-Intensity User	N/A
				High-Intensity User	N/A

N/A = not assessed

5 Risk Determination

5.1 Unreasonable Risk

5.1.1 Overview

In each risk evaluation under TSCA section 6(b), EPA determines whether a chemical substance presents an unreasonable risk of injury to health or the environment, under the conditions of use. These determinations do not consider costs or other non-risk factors. In making these determinations, EPA considers relevant risk-related factors, including, but not limited to: the effects of the chemical substance on health and human exposure to such substance under the conditions of use (including cancer and non-cancer risks); the effects of the chemical substance on the environment and environmental exposure under the conditions of use; the population exposed (including any potentially exposed or susceptible subpopulations (PESS)); the severity of hazard (including the nature of the hazard, the irreversibility of the hazard); and uncertainties. EPA also takes into consideration the Agency's confidence in the data used in the risk estimate. This includes an evaluation of the strengths, limitations and uncertainties associated with the information used to inform the risk estimate and the risk characterization. This approach is in keeping with the Agency's final rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726).[6]

Under TSCA, conditions of use are defined as the circumstances, as determined by the Administrator, under which the substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of. TSCA §3(4).

An unreasonable risk may be indicated when health risks under the conditions of use are identified by comparing the estimated risks with the risk benchmarks and where the risks affect the general population or PESS identified as relevant. For workers (which are one example of PESS), an unreasonable risk may be indicated when risks are not adequately addressed through expected use of workplace practices and exposure controls, including engineering controls or use of personal protective equipment (PPE). An unreasonable risk may also be indicated when environmental risks under the conditions of use are greater than environmental risk benchmarks. The risk estimates contribute to the evidence EPA uses to determine unreasonable risk.

EPA uses the term "indicates unreasonable risk" to indicate EPA concern for potential unreasonable risk. For non-cancer endpoints, "less than MOE benchmark" is used to indicate potential unreasonable risk; this occurs if an MOE value is less than the benchmark MOE (e.g., MOE 0.3 < benchmark MOE 30). For cancer endpoints, EPA uses the term "greater than risk benchmark" to indicate potential unreasonable risk; this occurs, for example, if the lifetime cancer risk value is greater than 1 in 10,000 (e.g., cancer risk value is $5x10^{-2}$ which is greater than the standard range of acceptable cancer risk

[6] This risk determination is being issued under TSCA section 6(b) and the terms used, such as unreasonable risk, and the considerations discussed are specific to TSCA. Other statutes have different authorities and mandates and may involve risk considerations other than those discussed here.

benchmarks of $1x10^{-4}$ to $1x10^{-6}$). For environmental endpoints, to indicate potential unreasonable risk EPA uses a risk quotient (RQ) value "greater than 1" (i.e., RQ >1). Conversely, EPA uses the term "does not indicate unreasonable risk" to indicate that it is unlikely that EPA has a concern for potential unreasonable risk. More details are described below.

The degree of uncertainty surrounding the MOEs, cancer risk or RQs is a factor in determining whether or not unreasonable risk is present. Where uncertainty is low, and EPA has high confidence in the hazard and exposure characterizations (for example, the basis for the characterizations is measured or monitoring data or a robust model and the hazards identified for risk estimation are relevant for conditions of use), the Agency has a higher degree of confidence in its risk determination.
EPA may also consider other risk factors, such as severity of endpoint, reversibility of effect, or exposure-related considerations, such as magnitude or number of exposures, in determining that the risks are unreasonable under the conditions of use. Where EPA has made assumptions in the scientific evaluation, whether or not those assumptions are protective will also be a consideration. Additionally, EPA considers the central tendency and high-end scenarios when determining the unreasonable risk. High-end risk estimates (i.e., 95th percentile) are generally intended to cover individuals or sub-populations with greater exposure (PESS) and central tendency risk estimates are generally estimates of average or typical exposure.

EPA may make a no unreasonable risk determination for conditions of use where the substance's hazard and exposure potential, or where the risk-related factors described previously, lead EPA to determine that the risks are not unreasonable.

5.1.2 Risks to Human Health

5.1.2.1 Determining Non-Cancer Risks

Margins of exposure (MOEs) are used in EPA's risk evaluations as a starting point to estimate non-cancer risks for acute and chronic exposures. The non-cancer evaluation refers to potential adverse health effects associated with health endpoints other than cancer, including to the body's organ systems, such as reproductive/developmental effects, cardiac and lung effects, and kidney and liver effects. The MOE is the point of departure (POD) (an approximation of the no-observed adverse effect level (NOAEL) or benchmark dose level (BMDL)) for a specific health endpoint divided by the exposure concentration for the specific scenario of concern. The benchmark for the MOE that is used accounts for the total uncertainty in a POD, including, as appropriate: (1) the variation in sensitivity among the members of the human population (i.e., intrahuman/intraspecies variability); (2) the uncertainty in extrapolating animal data to humans (i.e., interspecies variability); (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from sub-chronic to chronic exposure); and (4) the uncertainty in extrapolating from a lowest observed adverse effect level (LOAEL) rather than from a NOAEL. MOEs can provide a non-cancer risk profile by presenting a range of estimates for different non-cancer health effects for different exposure scenarios and are a widely recognized point estimate method for evaluating a range of potential non-cancer health risks from exposure to a chemical.

A calculated MOE that is less than the benchmark MOE indicates the possibility of risk to human health. Whether those risks are unreasonable will depend upon other risk-related factors, such as severity of endpoint, reversibility of effect, exposure-related considerations (e.g., duration, magnitude, frequency of exposure, population exposed), and the confidence in the information used to inform the hazard and exposure values. If the calculated MOE is greater than the benchmark MOE, generally it is less likely that there is risk.

Uncertainty factors (UFs) also play an important role in the risk estimation approach and in determining unreasonable risk. A lower benchmark MOE (e.g., 30) indicates greater certainty in the data (because fewer of the default UFs relevant to a given POD as described above were applied). A higher benchmark MOE (e.g., 1000) would indicate more uncertainty in risk estimation and extrapolation for the MOE for specific endpoints and scenarios. However, these are often not the only uncertainties in a risk evaluation.

5.1.3 Determining Environmental Risk

To assess environmental risk, EPA identifies and evaluates environmental hazard data for aquatic, sediment-dwelling, and terrestrial organisms exposed under acute and chronic exposure conditions. The environmental risk includes any risks that exceed benchmarks to the aquatic environment from levels of the evaluated chemical released to the environment (e.g., surface water, sediment, soil, biota) under the conditions of use, based on the fate properties, release potential, and reasonably available environmental monitoring and hazard data.

Environmental risks are estimated by calculating a RQ. The RQ is defined as:

RQ = Environmental Concentration / Effect Level

An RQ equal to 1 indicates that the exposures are the same as the concentration that causes effects. If the RQ is greater than 1, the exposure is greater than the effect concentration and there is potential for risk presumed. If the RQ is less than 1, the exposure is less than the effect concentration and unreasonable risk is not likely. The Concentrations of Concern or hazard value for certain aquatic organisms are used to calculate RQs for acute and chronic exposures. For environmental risk, EPA is more likely to determine that there is unreasonable risk if the RQ exceeds 1 for the conditions of use being evaluated. Consistent with EPA's human health evaluations, the RQ is not treated as a bright line and other risk-based factors may be considered (e.g., exposure scenario, uncertainty, severity of effect) for purposes of making a risk determination.

5.2 Risk Determination for NMP

EPA's determinations of unreasonable risk for specific conditions of use of NMP listed below are based on health risks to workers during occupational exposures, including occupational non-users in certain exposure scenarios; and health risks to consumers. With respect to cancer risks, as discussed in section 2.4.2.2 of the Problem Formulation of the Risk Evaluation for NMP, NMP is not mutagenic and is not considered carcinogenic so EPA did not conduct analysis of genotoxicity and cancer hazards during risk evaluation. For the conditions of use where EPA found no unreasonable risk, EPA describes the estimated risks in Section 4 (Table 4-49 and Table 4-50).

As described in section 3, significant risks associated with more than one adverse effect were identified for particular conditions of use. In the table below, EPA identifies either reproductive effects or adverse developmental effects as the unreasonable risk driver for the conditions of use, depending on whether acute or chronic exposure was assessed. The effects identified as the unreasonable risk driver vary because chronic exposures typically involve repeated doses, such as in an occupational setting, in contrast to acute exposures in a consumer setting.

EPA selected reduced fertility as the basis for evaluating risks from chronic exposures. This is described as reproductive toxicity in the risk determination and throughout the risk evaluation. EPA determined that this is an appropriate endpoint for evaluating chronic risk because it is a sensitive effect observed in a high-quality study and it is supported by robust evidence for a continuum of reproductive and developmental effects across several studies. EPA has selected fetal resorptions (mortality), an adverse developmental effect, as the basis for evaluating risks from acute exposures. EPA determined that this endpoint is the most applicable to assessing risks from acute exposures, where the risk of their occurrence is assumed to depend on exceedance of a threshold value for even a single day (i.e., peak concentration) rather than a time weighted average value and the magnitude of the exposure is considered more important for these effects under these study conditions.

The previous EPA assessment did not characterize dose-response for these fertility endpoints because the effect observed in one study was not replicated in more recent studies. However, together, the acute and chronic effects indicate a continuum of reproductive and developmental effects associated with NMP exposure. The complete basis for selection of endpoints is described in detail in section 3.2.5.1 (Selection of Endpoints for Dose-Response Assessment) and section 3.2.5.6 (Points of Departure for Human Health Hazard Endpoints).

As described below, risks to the environment, general population, occupational non-users (ONUs) and bystanders from consumer use either were not relevant for these conditions of use or were evaluated and found not to be unreasonable.

- **Environmental risks:** For all conditions of use, EPA did not identify any scenarios indicating unreasonable risk for aquatic, sediment-dwelling, or terrestrial organisms from exposures to NMP. NMP readily degrades under aerobic conditions and is not expected to persist in the environment. A screening level risk analysis for NMP in surface water and aquatic receptors resulted in RQs for the acute and chronic risk of 0.0022 and 0.85, respectively (Table 4-2). An RQ that does not exceed 1 indicates that the exposure concentrations of NMP are less than the concentrations that would cause an effect to organisms in the aquatic pathways. Because the RQ values do not exceed 1, and because EPA used a conservative screening level approach, these values indicate that the risks of NMP to the aquatic organisms are unlikely. In addition, NMP is unlikely to accumulate in sediment based on NMP's physical chemical properties. NMP is not expected to adsorb to sediment due to its water solubility and low partitioning to organic matter. Because NMP toxicity to sediment-dwelling organisms is expected to be comparable to that of aquatic organisms, minimal risks are anticipated for sediment-dwelling organisms. NMP exhibits low volatility and readily biodegrades under aerobic conditions; therefore, the concentrations in ambient air are unlikely to reach levels that would present risks for terrestrial organisms. As a result, EPA does not find unreasonable risks to the environment for the conditions of use for NMP.

- **General Population:** EPA is not including general population exposures in the risk evaluation for NMP. As explained in the Problem Formulation for the Risk Evaluation for NMP, general population exposures were determined to be outside the scope of the risk evaluation. EPA has determined that the existing regulatory programs and associated analytical processes adequately assess and effectively manage the risks of NMP that may be present in various media pathways (e.g. air, water, land) for the general population. For these cases, EPA believes that the TSCA risk evaluation should not focus on those exposure pathways, but rather on exposure pathways associated with TSCA conditions of use that are not subject to those regulatory processes, because the latter pathways are likely to represent the greatest areas of concern to EPA.

- **Occupational Non-Users:** EPA's exposure assessment includes estimates of NMP exposures to occupational non-users (ONUs). ONUs are located in the general vicinity near workers but are further from emissions sources. Unlike workers, ONUs do not have direct dermal contact with liquids. The estimates assume ONUs are not wearing respirators. While the difference between ONU exposures and workers directly handling the chemical generally cannot be quantified, EPA assumes that, in most cases, ONU inhalation exposures are expected to be lower than inhalation exposures for workers directly handling the chemical substance. To account for those instances where monitoring data or modeling did not distinguish between worker and ONU inhalation exposure estimates, EPA considered the central tendency risk estimate when determining ONU risk. As a result, while high-end chronic exposures indicate risks for ONUs, risk estimates for ONUs for the central tendency scenarios did not indicate risk. EPA determined that the conditions of use assessed did not present an unreasonable risk for ONUs.

- **Bystanders (to uses by consumers):** EPA's exposure assessment includes estimates of NMP exposures to bystanders (i.e. those located in the house during consumer product use) who do not have direct contact with NMP-containing consumer products. EPA did not identify risks to bystanders to consumer uses and has determined that the conditions of use assessed do not present an unreasonable risk to bystanders.

Table 5-1. NMP Risk Determinations by Conditions of Use

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
Manufacture	Domestic Manufacture	Domestic Manufacture	Section 6(b)(4)(A) unreasonable risk determination for domestic manufacture of NMP: - Does not present an unreasonable risk of injury to health (workers, occupational non-users). Exposure scenario with highest risk estimates: Reproductive effects from chronic inhalation and dermal exposure. Benchmark: MOE = 30 for reproductive effects.

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			Risk Estimate: MOE = 48 with workers using gloves (PF = 20) (high-end scenario) (Table 4-6). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium. Risk Considerations: While the chronic risk estimates for both central tendency and high-end exposure in the absence of PPE indicate risk, risk estimates for central tendency and high-end exposure do not indicate risk, when expected use of PPE was considered (gloves PF = 20) (Table 4-6). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.1. Estimated exposed population: 2,800 workers.
Manufacture	Import	Import	Section 6(b)(4)(A) unreasonable risk determination for manufacture – import of NMP: - Does not present an unreasonable risk of injury to health (workers, occupational non-users). Exposure scenario with highest risk estimate: Reproductive effects from chronic inhalation and dermal exposure. Benchmark: MOE = 30 for reproductive effects. Risk Estimate: MOE = 25 with workers using gloves (PF = 10) (high-end scenario) (Table 4-8). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium.

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			Risk Considerations: While the high-end scenario risk estimates indicate risk in the absence of PPE and when expected use of PPE was considered (gloves PF = 10), given the uncertainties in the model, these were not considered unreasonable risks (Table 4-8). While the chronic central tendency scenario risk estimate indicates risk in the absence of PPE, risk estimates for the central tendency scenarios do not indicate risk (MOE = 213) when expected use of PPE was considered (gloves PF = 10) (Table 4-8). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.2. Estimated exposed population: 1,100 workers.
Processing	Processing as a reactant or intermediate	Intermediate in Plastic Material and Resin Manufacturing and in Pharmaceutical and Medicine Manufacturing	Section 6(b)(4)(A) unreasonable risk determination for processing NMP as a reactant or intermediate in several manufacturing processes: - Does not present an unreasonable risk of injury to health (workers, occupational non-users). Exposure scenario with highest risk estimate: Reproductive effects from chronic inhalation and dermal exposure. Benchmark: MOE = 30 for reproductive effects. Risk Estimate: MOE = 143 with workers using gloves (PF = 10) (high-end scenario) (Table 4-10). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium. Risk Considerations: While the risk estimates for the chronic central tendency and high-end scenarios indicate risk in the absence of PPE, risk estimates for
		Other	

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			the central tendency and high-end scenarios do not indicate risk when expected use of PPE was considered (gloves PF = 10) (Table 4-10). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.3. Estimated exposed population: 5,400 workers.
Processing	Incorporated into formulation, mixture or reaction product	Adhesives and sealant chemicals in Adhesive Manufacturing	Section 6(b)(4)(A) unreasonable risk determination for processing NMP for incorporation into a formulation, mixture or reaction product, in several industrial sectors: - **Presents an unreasonable risk of injury to health (workers).** - Does not present an unreasonable risk of injury to health (occupational non-users). Unreasonable risk driver: Reproductive effects from chronic inhalation and dermal exposure. Driver Benchmark: MOE = 30 for reproductive effects. Risk Estimates: MOE = 6 with workers using gloves (PF = 10) (high-end scenario) (Table 4-12). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium to High. Risk Considerations: Worker unreasonable risk determination reflects the severity of the effects associated with chronic exposures, even in the presence of expected PPE. The high-end scenario risk estimates indicate risk even when expected use of PPE was considered (gloves PF = 10). While the
		Anti-adhesive agents in Printing and Related Support Activities	
		Paint additives and coating additives not described by other codes in Paint and Coating Manufacturing; and Print Ink Manufacturing	
		Plating agents and surface treating agents in Fabricated Metal Product Manufacturing	
		Processing aids not otherwise listed in Plastic Material and Resin Manufacturing	
		Solvents (for cleaning or degreasing) in Non-Metallic Mineral Product Manufacturing; Machinery Manufacturing; Plastic Material and Resin	

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
		Manufacturing; Primary Metal Manufacturing; Soap, Cleaning Compound and Toilet Preparation Manufacturing; Transportation Equipment Manufacturing; All Other Chemical Product and Preparation Manufacturing; Printing and Related Support Activities; Services; Wholesale and Retail Trade	chronic central tendency scenario risk estimate indicates risk in the absence of PPE, risk estimates for the central tendency scenarios do not indicate risk (MOE = 291) when expected use of PPE was considered (gloves PF = 10) (Table 4-12). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.4. Estimated exposed population: 1,900 workers.
		Solvents (which become part of product formulation or mixture) in Electrical Equipment, Appliance and Component Manufacturing; Other Manufacturing; Paint and Coating Manufacturing; Print Ink Manufacturing; Soap, Cleaning Compound and Toilet Preparation Manufacturing; Transportation Equipment Manufacturing; All Other Chemical Product and Preparation Manufacturing; Printing and Related Support Activities; Wholesale and Retail Trade	
		Surface active agents in Soap, Cleaning Compound and Toilet Preparation Manufacturing	
		Other uses in Oil and Gas Drilling, Extraction and Support Activities; Plastic Material and Resin Manufacturing; Services	
Processing	Incorporated into articles	Lubricants and lubricant additives in Machinery Manufacturing	Section 6(b)(4)(A) unreasonable risk determination for processing NMP for incorporation into articles as lubricants and lubricant additives in machinery manufacturing:

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			-Presents an unreasonable risk of injury to health (workers). - Does not present an unreasonable risk of injury to health (occupational non-users). Unreasonable risk driver: Reproductive effects from chronic inhalation and dermal exposure. Driver Benchmark: MOE = 30 for reproductive effects. Risk Estimate: MOE = 7 with workers using gloves (PF = 10) (high-end scenarios for spray, dip, or brush applications) (Table 4-18). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium. Risk Considerations: Worker unreasonable risk determination reflects the severity of the effects associated with chronic exposures, even in the presence of expected PPE. The high-end scenario risk estimates indicate risk even when expected use of PPE was considered (gloves PF = 10). While the chronic central tendency scenario risk estimate indicates risk in the absence of PPE, risk estimates for the central tendency scenarios do not indicate risk (MOE = 44) when expected use of PPE was considered (gloves PF = 10) (Table 4-18). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.5. Estimated exposed population: 530,000 workers.
Processing	Incorporated into articles	Paint additives and coating additives not described by	Section 6(b)(4)(A) unreasonable risk determination for processing NMP for incorporation into articles as

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
		other codes in Transportation Equipment Manufacturing	paint additives and coating additives not described by other codes in Transportation Equipment Manufacturing: - **Presents an unreasonable risk of injury to health (workers).** - Does not present an unreasonable risk of injury to health (occupational non-users). Unreasonable risk driver: Reproductive effects from chronic inhalation and dermal exposure. Driver Benchmark: MOE = 30 and for reproductive effects. Risk Estimates: MOE = 12 with workers using gloves (PF = 10) for spray, dip, roll curtain or brush applications (high-end scenarios) (Table 4-14). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium. Risk Considerations: Worker unreasonable risk determination reflects the severity of the effects associated with chronic exposures, even in the presence of expected PPE. For chronic exposures, the high-end scenario risk estimates indicate risk in the absence of PPE and even when expected use of PPE was considered (gloves PF = 10). Risk estimates for the central tendency scenarios did not indicate risk (MOEs = 1294 to 194) in the absence of PPE (Table 4-14). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the use, as well as exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.7. Estimated exposed population: 2,000,000 workers.

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
Processing	Incorporated into articles	Solvents (which become part of product formulation or mixture), including in Textiles, Apparel and Leather Manufacturing	Section 6(b)(4)(A) unreasonable risk determination for processing NMP for incorporation into articles as a solvent (which becomes part of product formulation or mixture), including in textiles, apparel and leather manufacturing: - **Presents an unreasonable risk of injury to health (workers).** - Does not present an unreasonable risk of injury to health (occupational non-users). Unreasonable risk driver: Reproductive effects from chronic inhalation and dermal exposure. Driver Benchmark: MOE = 30 for reproductive effects. Risk Estimate: MOE = 6 with workers using gloves (PF = 10) (high-end scenario) (Table 4-12). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium. Risk Considerations: Worker unreasonable risk determination reflects the severity of the effects associated with chronic exposures, even in the presence of expected PPE. The high-end scenario risk estimates indicate risk even when expected use of PPE was considered (gloves PF = 10). Risk estimates for the high-end acute exposures indicate risk in the absence of PPE. While the chronic central tendency scenario risk estimate indicates risk in the absence of PPE, risk estimates for the central tendency scenarios do not indicate risk (MOE = 291) when expected use of PPE was considered (gloves PF =10) (Table 4-12). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			scenario inputs and models for this condition of use are in Section 2.4.1.2.4. Estimated exposed population: 1,900 workers.
Processing	Incorporated into articles	Other, including in Plastic Product Manufacturing	Section 6(b)(4)(A) unreasonable risk determination for processing NMP for incorporation into articles in other sectors, including in plastic product manufacturing: - Does not present an unreasonable risk of injury to health (workers, occupational non-users). Exposure scenario with highest risk estimate: Reproductive effects from chronic inhalation and dermal exposure. Benchmark: MOE = 30 for reproductive effects. Risk Estimate: MOE = 143 with workers using gloves (PF = 10) (high-end scenario) (Table 4-10). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium. Risk Considerations: While the risk estimates for the chronic central tendency and high-end scenarios indicate risk in the absence of PPE, risk estimates for the central tendency and high-end scenarios do not indicate risk when expected use of PPE was considered (gloves PF = 10) (Table 4-10). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.3. Estimated exposed population: 5,400 workers.

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
Processing	Repackaging	Wholesale and Retail Trade	Section 6(b)(4)(A) unreasonable risk determination for processing of NMP for repackaging for wholesale and retail trade: -Does not present an unreasonable risk of injury to health (workers, occupational non-users). Exposure scenario with highest risk estimates: Reproductive effects from chronic inhalation and dermal exposure. Driver Benchmark: MOE = 30 for reproductive effects. Risk Estimate: MOE = 25 with workers using gloves (PF = 10) (high-end scenario) (Table 4-8). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium. Risk Considerations: While the high-end scenario risk estimates indicate risk in the absence of PPE and when expected use of PPE was considered (gloves PF = 10), given the uncertainties in the model, these were not considered unreasonable risks (Table 4-8). While the chronic central tendency scenario risk estimate indicates risk in the absence of PPE, risk estimates for the central tendency scenarios do not indicate risk (MOE = 213) when expected use of PPE was considered (gloves PF = 10) (Table 4-8). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.2. Estimated exposed population: 1,100 workers.
Processing	Recycling	Recycling	Section 6(b)(4)(A) unreasonable risk determination for processing – recycling of NMP:

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			-Does not present an unreasonable risk of injury to health (workers, occupational non-users). Exposure scenario with highest risk estimate: Reproductive effects from chronic inhalation and dermal exposure. Benchmark: MOE = 30 for reproductive effects. Risk Estimate: MOE = 43 with workers using gloves (PF = 5) (high-end scenario) (Table 4-36). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium. Risk Considerations: While the chronic high-end scenario risk estimates indicate risk in the absence of PPE, risk estimates for these scenarios do not indicate risk when use of PPE was considered (gloves PF = 5). For this condition of use, EPA expects gloves PF = 20, due to the recycling of solvents. For NMP, risks are not indicated with gloves PF = 5. While the chronic central tendency scenario risk estimate indicates risk in the absence of PPE, risk estimates for the central tendency scenarios do not indicate risk when expected use of PPE was considered (gloves PF = 5) (Table 4-36). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.16. Estimated exposed population: 200 workers.
Distribution in commerce	Distribution in Commerce	Distribution in Commerce	Section 6(b)(4)(A) unreasonable risk determination for distribution in commerce of NMP: - Does not present an unreasonable risk of injury to health (workers, occupational non-users)

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			Risk Considerations: A quantitative evaluation of the distribution of NMP was not included in the risk evaluation because exposures and releases from distribution were considered within each condition of use.
Industrial and commercial use	Paints and coatings	Paint and coating removers	Section 6(b)(4)(A) unreasonable risk determination for industrial and commercial use of NMP in paint and coating removers and in adhesive removers: **-Presents an unreasonable risk of injury to health (workers).** - Does not present an unreasonable risk of injury to health (occupational-non users). Unreasonable risk driver: Reproductive effects from chronic inhalation and dermal exposure. Driver Benchmark: MOE = 30 for reproductive effects. Risk Estimates - Workers: MOE = 6 with workers using gloves (PF = 10) for miscellaneous removal (high-end scenario), MOE = 10 with workers using gloves (PF = 10) for graffiti removal (high-end scenario), (Table 4-20). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium to High. Risk Considerations: The worker unreasonable risk determination reflects the severity of the effects associated with chronic exposures, even in the presence of expected PPE for workers. For workers, the chronic high-end scenario risk estimates for inhalation and dermal exposures indicate risk even when expected use of PPE was considered (gloves PF = 10) (Table 4-20). For workers, while the chronic central tendency scenario risk estimate indicates risk in the absence of PPE, risk estimates for the central tendency scenarios do not indicate risk when expected use of PPE was considered (gloves PF =10) (Table 4-20). For occupational non-users (ONUs), while the chronic high-end scenario risk
		Adhesive removers	

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			estimates for inhalation exposures and vapor-through-skin uptake indicate risk, the chronic central tendency scenario risk estimate does not indicate risk. In contrast to the worker risk estimates, which include dermal exposure, the risk estimates for occupational non-users use exclusively inhalation and vapor-through skin exposures. (Table 4-37). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. Data sources did not usually indicate whether NMP exposure concentrations were for occupational users or ONUs. For inhalation and vapor-through-skin exposures, if EPA cannot distinguish ONU exposures from workers, EPA assumes that ONUs are exposed to lower air concentrations compared to workers because they are expected to be located a greater distance from the worker handling the NMP-containing product. To account for those instances where monitoring data or modeling did not distinguish between worker and ONU inhalation exposure estimates, EPA considered the central tendency risk estimate when determining ONU risk. (Table 4-37). The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.6. Estimated exposed population: 2,000,000 workers.
Industrial and commercial use	Paints and coatings	Lacquers, stains, varnishes, primers and floor finishes	Section 6(b)(4)(A) unreasonable risk determination for industrial and commercial use of NMP in paint and coatings (lacquers, stains, varnishes, primers and floor finishes, and powder coatings, surface preparation), in paint additives and coating additives not described by other codes in several manufacturing sectors, and in adhesives and sealants, several types: **- Presents an unreasonable risk of injury to health (workers).**
		Powder coatings (surface preparation)	
	Paint additives and coating additives not	Use in Computer and Electronic Product Manufacturing, Construction, Fabricated Metal Product Manufacturing, Machinery	

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
	described by other codes	Manufacturing, Other Manufacturing, Paint and Coating Manufacturing, Primary Metal Manufacturing, Transportation Equipment Manufacturing, Wholesale and Retail Trade	- Does not present an unreasonable risk of injury to health (occupational non-users). Unreasonable risk driver: Reproductive effects from chronic inhalation and dermal exposure. Driver Benchmark: MOE = 30 for reproductive effects Risk Estimates: MOE = 12 with workers using gloves (PF = 10) for spray, roll/curtain, dip, or brush applications (high-end scenarios) (Table 4-14). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium to High. Risk Considerations: Worker unreasonable risk determination reflects the severity of the effects associated with chronic exposures, even in the presence of expected PPE. The high-end scenario risk estimates indicate risk even when expected use of PPE was considered (gloves PF = 10). (Table 4-14). Risk estimates for the central tendency scenarios did not indicate risk in the absence of PPE (Table 4-14). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.7. Estimated exposed population: 2,000,000 workers.
	Adhesives and sealants	Adhesives and sealant chemicals including binding agents	
		Single component glues and adhesives, including lubricant adhesives	
		Two-component glues and adhesives, including some resins	
Industrial and commercial use	Solvents (for cleaning or degreasing)	Use in Electrical Equipment, Appliance and Component Manufacturing	Section 6(b)(4)(A) unreasonable risk determination for industrial and commercial use of NMP as a solvent (for cleaning or degreasing) use in electrical equipment, appliance and component manufacturing and for other uses in manufacturing lithium ion batteries:
	Other uses	Lithium ion batteries [cd]	

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			- Presents an unreasonable risk of injury to health (workers). - Does not present an unreasonable risk of injury to health (occupational non-users). Unreasonable risk driver: Reproductive effects from chronic inhalation and dermal exposure. Driver Benchmark: MOE = 30 for reproductive effects. Risk Estimates (workers using gloves (PF = 10), (high-end scenario): container handling: MOE = 6; drum handling: MOE = 6; fab worker: MOE = 4; maintenance: MOE = 4; truck unloading: MOE = 6; waste truck unloading: MOE = 7. (Table 4-28). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium to High Risk Considerations: For all workers, the worker unreasonable risk determination reflects the severity of the effects associated with chronic exposures, even in the presence of expected PPE. The high-end scenario risk estimates indicate risk even when expected use of PPE was considered (gloves PF = 10). The chronic central tendency scenario risk estimates indicate risk in the absence of PPE. The chronic central tendency scenario risk estimates also indicate risks with expected use of PPE for specific activities (small container handling, virgin NMP truck unloading and waste truck unloading) but not for other activities (container handling drums, fab workers, maintenance) (gloves PF = 10) (Table 4-28). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.8. Estimated exposed population: 660,000 workers.
Industrial and commercial use	Ink, toner, and colorant products	Printer ink	Section 6(b)(4)(A) unreasonable risk determination for industrial and commercial use of NMP in ink, toner, and colorant products, including printer ink and inks in writing equipment: -Does not present an unreasonable risk of injury to health (workers, occupational non-users). Exposure scenario with highest risk estimate: Reproductive effects from chronic inhalation and dermal exposure. Benchmark: MOE = 30 for reproductive effects. Risk Estimate: MOE = 48 with workers using gloves (PF = 5) (high-end scenario) (Table 4-16). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium to High. Risk Considerations: While the high-end scenario risk estimates for printing indicate risk in the absence of PPE, risk estimates for this scenario do not indicate risk when expected use of PPE was considered (gloves PF = 5). Risk estimates for the central tendency scenarios did not indicate risk in the absence of PPE (Table 4-16). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.9. Estimated exposed population: 53,000 workers.
		Inks in writing equipment	

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
Industrial and commercial use	Processing aids, specific to petroleum production	Petrochemical Manufacturing	Section 6(b)(4)(A) unreasonable risk determination for industrial and commercial use of NMP in processing aids, specific to petroleum production in petrochemical manufacturing, and other uses in oil and gas drilling and pharmaceutical and medicine manufacturing: -Does not present an unreasonable risk of injury to health (workers, occupational non-users). Exposure scenario with highest risk estimate: Reproductive effects from chronic inhalation and dermal exposure. Benchmark: MOE = 30 for reproductive effects. Risk Estimate: MOE = 143 with workers using gloves (PF = 10) (high-end scenario) (Table 4-10). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium. Risk Considerations: While the risk estimates for the chronic central tendency and high-end scenarios indicate risk in the absence of PPE, risk estimates for the central tendency and high-end scenarios do not indicate risk when expected use of PPE was considered (gloves PF = 10) (Table 4-10). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.3. Estimated exposed population: 5,400 workers.
	Other uses	Other uses in Oil and Gas Drilling, Extraction and Support Activities	
		Pharmaceutical and Medicine Manufacturing - functional fluids (closed systems)	
Industrial and commercial use	Other uses	Soldering materials	Section 6(b)(4)(A) unreasonable risk determination for industrial and commercial use of NMP as soldering material:

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			-Does not present an unreasonable risk of injury to health (workers, occupational non-users). Exposure scenario with highest risk estimate: Reproductive effects from chronic inhalation and dermal exposure. Benchmark: MOE = 30 for reproductive effects. Risk Estimate: MOE = 270 with workers using gloves (PF = 10) (high-end scenario) (Table 4-30). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Low to Medium. Risk Considerations: While the high-end chronic scenario risk estimate indicates risk in the absence of PPE, risk estimates for this scenario do not indicate risk when expected use of PPE was considered (gloves PF = 10) (Table 4-30). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.10. Estimated exposed population: 4,000,000 workers.
Industrial and commercial use	Other uses	Anti-freeze and de-icing products Automotive care products Lubricants and greases	Section 6(b)(4)(A) unreasonable risk determination for industrial and commercial use of NMP in anti-freeze and de-icing products, automotive care products, and lubricants and greases: **- Presents an unreasonable risk of injury to health (workers)** - Does not present an unreasonable risk of injury to health (occupational non-users). Unreasonable risk driver: Workers: Reproductive effects from chronic inhalation and dermal exposure.

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			Driver Benchmarks (workers and occupational non-users): MOE = 30 for reproductive effects. Risk Estimates: MOE = 10 with workers using gloves (PF = 10) (high-end scenario) (Table 4-24). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium. Risk Considerations: The worker unreasonable risk determination reflects the severity of the effects associated with chronic exposures, even in the presence of expected PPE for workers. For workers, the chronic high-end scenario risk estimates for inhalation and dermal exposures indicate risk even when expected use of PPE was considered (gloves PF = 10). (Table 4-24). For workers, risk estimates for the central tendency scenarios did not indicate risk in the absence of PPE (Table 4-24). For occupational non-users (ONUs), while the chronic high-end scenario risk estimates for inhalation exposures and vapor-through-skin uptake indicates risks, the chronic central tendency scenario risk estimate does not indicate risk. In contrast to the worker risk estimates, which include dermal exposure, the risk estimates for occupational non-users use exclusively inhalation and vapor-through-skin exposures. (Table 4-37). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. Inhalation data sources did not usually indicate whether NMP exposure concentrations were for occupational users or ONUs. For inhalation and vapor-through-skin exposures, if EPA cannot distinguish ONU exposures from workers, EPA assumes that ONUs are exposed to lower air concentrations compared to workers

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			because they are expected to be located a greater distance from the worker handling the NMP-containing product. To account for those instances where monitoring data or modeling did not distinguish between worker and ONU inhalation exposure estimates, EPA considered the central tendency risk estimate when determining ONU risk. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.11. Estimated exposed population: 910,000 workers.
Industrial and commercial use	Other uses	Metal products not covered elsewhere	Section 6(b)(4)(A) unreasonable risk determination for industrial and commercial use of NMP in metal products and lubricants and lubricant additives, including hydrophilic coatings: **-Presents an unreasonable risk of injury to health (workers).** - Does not present an unreasonable risk of injury to health (occupational non-users). Unreasonable risk driver: Reproductive effects from chronic inhalation and dermal exposure. Driver Benchmark: MOE = 30 for reproductive effects. Risk Estimate: MOE = 7 with workers using gloves (PF = 10) for spray, dip, or brush applications (high-end scenarios) (Table 4-18). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium. Risk Considerations: Worker unreasonable risk determination reflects the severity of the effects associated with chronic exposures, even in the presence of expected PPE. The high-end scenario risk estimates indicate risk even when expected use of PPE was considered (gloves PF = 10). While the chronic central tendency scenario risk estimate indicates risk in the absence of PPE, risk estimates for the central tendency scenarios do not indicate risk when expected use of PPE was considered (gloves
		Lubricant and lubricant additives, including hydrophilic coatings	

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			PF = 10) (Table 4-18). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.5. Estimated exposed population: 530,000 workers.
Industrial and commercial use	Other uses	Laboratory chemicals	Section 6(b)(4)(A) unreasonable risk determination for industrial and commercial use of NMP as laboratory chemical: - **Presents an unreasonable risk of injury to health (workers).** - Does not present an unreasonable risk of injury to health (occupational non-users). Unreasonable risk driver: Reproductive effects from chronic inhalation and dermal exposure. Driver Benchmark: MOE = 30 for reproductive effects. Risk Estimate: MOE = 6 with workers using gloves (PF = 10) (high-end scenario) (Table 4-26). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium. Risk Considerations: Worker unreasonable risk determination reflects the severity of the effects associated with chronic exposures, even in the presence of expected PPE. The high-end scenario risk estimates indicate risk even when expected use of PPE was considered (gloves PF = 10). (Table 4-26). While the chronic central tendency scenario risk estimate indicates risk in the absence of PPE, risk estimates for the central tendency scenarios do not indicate risk when expected use of PPE was

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			considered (gloves PF =10) (Table 4-26). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.12. Estimated exposed population: 420,000 workers.
Industrial and commercial use	Other uses	Cleaning and furniture care products, including wood cleaners, gasket removers	Section 6(b)(4)(A) unreasonable risk determination for industrial and commercial use of NMP in cleaning and furniture care products, including wood cleaners, gasket removers: **-Presents an unreasonable risk of injury to health (workers).** - Does not present an unreasonable risk of injury to health (occupational non-users). Unreasonable risk driver: Reproductive effects from chronic inhalation and dermal exposure. Driver Benchmark: MOE = 30 for reproductive effects. Risk Estimates: MOE = 6 for workers using gloves (PF = 10) for dip cleaning and spray/wipe cleaning (high-end scenario) (Table 4-22). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium to High. Risk Considerations: Worker unreasonable risk determination reflects the severity of the effects associated with chronic exposures, even in the presence of expected PPE. The high-end scenario risk estimates indicate risk even when expected use of PPE was considered (gloves PF =10). (Table 4-22). The chronic central tendency risk estimate for dip cleaning and spray/wipe cleaning do not indicate

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			risk when expected use of PPE was considered (gloves PF = 10) (Table 4-22). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.13. Estimated exposed population: 190,000 workers.
Industrial and commercial use	Other uses	Fertilizer and other agricultural chemical manufacturing - processing aids and solvents	Section 6(b)(4)(A) unreasonable risk determination for industrial and commercial use of NMP in fertilizer and other agricultural chemical manufacturing: -Does not present an unreasonable risk of injury to health (workers, occupational non-users). Exposure scenario with highest risk estimate: Reproductive effects from chronic inhalation and dermal exposure. Benchmark: MOE = 30 for reproductive effects. Risk Estimate: MOE = 38 for workers using gloves (PF = 5) (high-end scenario) (Table 4-32). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium. Risk Considerations: While the high-end scenario risk estimates indicate risk in the absence of PPE, risk estimates for these scenarios do not indicate risk when expected use of PPE was considered (gloves PF = 5). Risk estimates for the central tendency scenarios did not indicate risk in the absence of PPE (Table 4-32). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.14. Estimated exposed population: 1,300,000 workers.
Industrial and commercial use	Other uses	Wood preservatives	Section 6(b)(4)(A) unreasonable risk determination for industrial and commercial use of NMP as a wood preservative: -Does not present an unreasonable risk of injury to health (workers, occupational non-users). Exposure scenario with highest risk estimate: Reproductive effects from chronic inhalation and dermal exposure. Benchmark: MOE = 30 for reproductive effects. Risk Estimate: MOE = 52 for workers without gloves (high-end scenario) (Table 4-34). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium. Risk Considerations: Risk estimates for all acute and chronic inhalation and dermal exposures (high-end and central tendency) do not indicate risk (Table 4-33 and Table 4-34). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.15.

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			Estimated exposed population: 380,000 workers.
Consumer use	Paints and coatings	Paint and coating removers	Section 6(b)(4)(A) unreasonable risk determination for consumer use of NMP in paint and coating removers: -**Presents an unreasonable risk of injury to health (consumers).** Unreasonable risk driver: Developmental adverse effects from acute inhalation and dermal exposure. Driver Benchmark: MOE = 30 for developmental effects. Risk Estimate: MOE = 22 (high intensity use) (Table 4-44). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium to High. Risk Considerations: Consumer unreasonable risk determination reflects the severity of the effects associated with acute exposures. The high intensity use scenario risk estimates indicate risk. Risk estimates for the medium intensity use scenarios of acute inhalation and dermal exposures did not indicate risk. (Table 4-44). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for Consumer Conditions of Use are in Section 2.4.2. Estimated exposed populations: There is uncertainty regarding the number of consumers exposed under the consumer conditions of use and the nature and extent of the consumer use of products containing NMP. EPA provides information in Table 2-69 on

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			NMP-containing consumer products used for the exposure assessment.
Consumer use	Paints and coatings	Adhesive removers	Section 6(b)(4)(A) unreasonable risk determination for consumer use of NMP in adhesive removers: -Does not present an unreasonable risk of injury to health (consumers and bystanders to consumer use). Exposure scenario with highest risk estimate: Developmental adverse effects from acute inhalation and dermal exposure. Benchmark: MOE = 30 for developmental effects. Risk Estimate: MOE = 36 (high intensity use) (Table 4-39). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium to High. Risk Considerations: Risk estimates for all acute inhalation and dermal exposures do not indicate risk (Table 4-39). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for Consumer Conditions of Use are in Section 2.4.2. Estimated exposed populations: There is uncertainty regarding the number of consumers exposed under the consumer conditions of use and the nature and extent of the consumer use of products containing NMP. EPA provides information in Table 2-69 on NMP-containing consumer products used for the exposure assessment.
Consumer use	Paints and coatings	Lacquers, stains, varnishes, primers and floor finishes	Section 6(b)(4)(A) unreasonable risk determination for consumer use of NMP in lacquers, stains, varnishes, primers and floor finishes:

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			-Does not present an unreasonable risk of injury to health (consumers and bystanders to consumer use). Exposure scenario with highest risk estimate: Developmental adverse effects from acute inhalation and dermal exposure. Benchmark: MOE = 30 for developmental effects. Risk Estimate: MOE = 111 (high intensity use) (Table 4-43). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium to High. Risk Considerations: Risk estimates for all acute inhalation and dermal exposures do not indicate risk (Table 4-43). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for Consumer Conditions of Use are in Section 2.4.2. Estimated exposed populations: There is uncertainty regarding the number of consumers exposed under the consumer conditions of use and the nature and extent of the consumer use of products containing NMP. EPA provides information in Table 2-69 on NMP-containing consumer products used for the exposure assessment.
Consumer use	Paint additives and coating additives not described by other codes	Paints and Arts and Crafts Paints	Section 6(b)(4)(A) unreasonable risk determination for consumer use of NMP in paint additives and coating additives not described by other codes, paints, and arts and crafts paints: - Does not present an unreasonable risk of injury to health (consumers and bystanders to consumer use).

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			Exposure scenario with highest risk estimate: Developmental adverse effects from acute inhalation and dermal exposure. Benchmark: MOE = 30 for developmental effects. Risk Estimate: MOE = 152 (paints, high intensity use) (Table 4-42). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium to High. Risk Considerations: Risk estimates for all acute inhalation and dermal exposures do not indicate risk (Table 4-42). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for Consumer Conditions of Use are in Section 2.4.2. Estimated exposed populations: There is uncertainty regarding the number of consumers exposed under the consumer conditions of use and the nature and extent of the consumer use of products containing NMP. EPA provides information in Table 2-69 on NMP-containing consumer products used for the exposure assessment.
Consumer use	Adhesives and sealants	Single component glues and adhesives, including lubricant adhesives	Section 6(b)(4)(A) unreasonable risk determination for consumer use of NMP as adhesive and sealant, single component glues and adhesives, including lubricant adhesives and two-component glues and adhesives, including some resins: - Does not present an unreasonable risk of injury to health (consumers and bystanders to consumer use). Exposure scenario with highest risk estimate: Developmental adverse effects from acute inhalation and dermal exposure.
		Two-component glues and adhesives, including some resins	

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			Benchmark: MOE = 30 for developmental effects. Risk Estimate: MOE = 38 (adhesives, high intensity use) (Table 4-38). Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium to High. Risk Considerations: Risk estimates for all acute inhalation and dermal exposures do not indicate risk (Table 4-38). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for Consumer Conditions of Use are in Section 2.4.2. Estimated exposed populations: There is uncertainty regarding the number of consumers exposed under the consumer conditions of use and the nature and extent of the consumer use of products containing NMP. EPA provides information in Table 2-69 on NMP-containing consumer products used for the exposure assessment.
Consumer use	Other uses	Automotive care products	Section 6(b)(4)(A) unreasonable risk determination for consumer use, other use as automotive care products of NMP: - Does not present an unreasonable risk of injury to health (consumers and bystanders to consumer use). Exposure scenario with highest risk estimate: Developmental adverse effects from acute inhalation and dermal exposure. Benchmark: MOE = 30 for developmental effects. Risk Estimate: MOE = 50 (auto interior liquid cleaner, high intensity use) (Table 4-40).

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			Systematic Review confidence rating (hazard): High. Systematic Review confidence rating (exposure): Medium to High. Risk Considerations: Risk estimates for all acute inhalation and dermal exposures do not indicate risk (Table 4-40). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for Consumer Conditions of Use are in Section 2.4.2. Estimated exposed populations: There is uncertainty regarding the number of consumers exposed under the consumer conditions of use and the nature and extent of the consumer use of products containing NMP. EPA provides information in Table 2-69 on NMP-containing consumer products used for the exposure assessment.
Consumer use	Other uses	Cleaning and furniture care products, including wood cleaners, gasket removers	Section 6(b)(4)(A) unreasonable risk determination for consumer use of NMP in other uses as cleaning and furniture care products, including wood cleaners, gasket removers: **- Presents an unreasonable risk of injury to health (consumers).** Unreasonable risk driver: Developmental adverse effects from acute inhalation and dermal exposure. Driver Benchmark: MOE = 30 for developmental effects. Risk Estimate: MOE = 16 (cleaners/degreasers, high intensity use); MOE = 13 (engine cleaner/degreaser, high intensity use) (Table 4-41). Systematic Review confidence rating (hazard): High.

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			Systematic Review confidence rating (exposure): Medium to High. Risk Considerations: Consumer unreasonable risk determination reflects the severity of the effects associated with acute exposures. The high intensity use scenario risk estimates indicate risk. Risk estimates for the medium intensity use scenarios of acute inhalation and dermal exposures did not indicate risk. (Table 4-41). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for Consumer Conditions of Use are in Section 2.4.2. Estimated exposed populations: There is uncertainty regarding the number of consumers exposed under the consumer conditions of use and the nature and extent of the consumer use of products containing NMP. EPA provides information in Table 2-69 on NMP-containing consumer products used for the exposure assessment.
Consumer use	Other uses	Lubricant and lubricant additives, including hydrophilic coatings	Section 6(b)(4)(A) unreasonable risk determination for consumer use of NMP in other uses as lubricant and lubricant additives, including hydrophilic coatings: - Does not present an unreasonable risk of injury to health (consumers and bystanders to consumer use). Exposure scenario with highest risk estimate: Developmental adverse effects from acute inhalation and dermal exposure. Benchmark: MOE = 30 for developmental effects. Risk Estimate: MOE = 76 (spray lubricant, high intensity use) (Table 4-41). Systematic Review confidence rating (hazard): High.

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
			Systematic Review confidence rating (exposure): Medium to High. Risk Considerations: Risk estimates for all acute inhalation and dermal exposures do not indicate risk (Table 4-41). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for Consumer Conditions of Use are in Section 2.4.2. Estimated exposed populations: There is uncertainty regarding the number of consumers exposed under the consumer conditions of use and the nature and extent of the consumer use of products containing NMP. EPA provides information in Table 2-69 on NMP-containing consumer products used for the exposure assessment.
Disposal	Disposal	Industrial pre-treatment Industrial wastewater treatment Publicly owned treatment works (POTW) Underground injection	Section 6(b)(4)(A) unreasonable risk determination for disposal of NMP: - Does not present an unreasonable risk of injury to health (workers, occupational non-users). Exposure scenario with highest risk estimate: Developmental adverse effects or reproductive effects from chronic inhalation and dermal exposure. Benchmark: MOE = 30 for developmental effects. Risk Estimate: MOE = 43 with workers using gloves (PF = 5) (high-end scenario) (Table 4-36). Systematic Review confidence rating (hazard): High.

Condition of Use			Unreasonable Risk Determination[1,2,3]
Life Cycle Stage	**Category**	**Sub-Category**	
		Landfill (municipal, hazardous or other land disposal)	Systematic Review confidence rating (exposure): Medium to High. Risk Considerations: While the risk estimates for the central tendency and high-end scenarios indicate risk in the absence of PPE, risk estimates for these scenarios do not indicate risk when expected use of PPE was considered (gloves PF=5). (Table 4-35 and Table 4-36). EPA relied on data, models, or a combination to estimate exposure and then estimate risk from NMP for this condition of use. Relevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP. The primary limitations of the exposure scenario inputs and models for this condition of use are in Section 2.4.1.2.16. Estimated exposed population: 200 workers.
		Emissions to air	
		Incinerators (municipal and hazardous waste)	

[1] EPA expects there is compliance with federal and state laws, such as worker protection standards, unless case-specific facts indicate otherwise, and therefore existing OSHA regulations for worker protection and hazard communication will result in use of appropriate PPE consistent with the applicable SDSs in a manner adequate to protect them.
[2] EPA recognizes that it may not be realistic to assume PPE is not worn in workplaces with higher end exposures or that PPE is ineffective. This is a health protective assumption EPA incorporated into the estimates for the high-end exposure scenario.
[3] For many OESs, the high-end surface area assumption of contact over the full area of two hands likely overestimates exposures.

6896

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APPENDICES

Appendix A REGULATORY HISTORY

A.1 Federal Laws and Regulations

Table_Apx A-1. Federal Laws and Regulations

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
EPA Regulations		
Toxic Substances Control Act (TSCA) – Section 6(a)	If EPA evaluates the risk of a chemical substance, in accordance with TSCA Section 6(b)(A), and concludes that the manufacture (including import), processing, distribution in commerce, disposal of such chemical substance, or any combination of these activities, presents an unreasonable risk of injury to human health or the environment, then EPA shall, by rule, take one or more of the actions described in TSCA Section 6(a)(1)-(7) to ensure the chemical substance no longer presents an unreasonable risk.	Proposed rule (82 FR 7464) regulating NMP uses in paint and coating removal
Toxic Substances Control Act (TSCA) – Section 6(b)	Directs EPA to promulgate regulations to establish processes for prioritizing chemical substances and conducting risk evaluations on priority chemical substances. In the meantime, EPA was required to identify and begin risk evaluations on 10 chemical substances drawn from the 2014 update of the TSCA Work Plan for Chemical Assessments.	NMP is on the initial list of 10 chemical substances to be evaluated for unreasonable risk of injury to health or the environment (81 FR 91927, December 19, 2016)
Toxic Substances Control Act (TSCA) – Section8(a)	The TSCA section 8(a) Chemical Data Reporting (CDR) Rule requires manufacturers (including importers) to give EPA basic exposure-related information on the types, quantities and uses of chemical substances produced	NMP manufacturing, importing, processing and use information is reported under the Chemical Data Reporting (CDR) rule (76 FR 50816, August 16, 2011).

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
	domestically and imported into the US.	
Toxic Substances Control Act (TSCA) – Section8(b)	EPA must compile, keep current and publish a list (the TSCA Inventory) of each chemical substance manufactured, processed, or imported in the United States.	NMP was on the initial TSCA Inventory and therefore was not subject to EPA's new chemicals review process (60 FR 16309, March 29, 1995).
Toxic Substances Control Act (TSCA) – Section 8(e)	Manufacturers (including importers), processors and distributors must immediately notify EPA if they obtain information that supports the conclusion that a chemical substance or mixture presents a substantial risk of injury to health or the environment.	Seven notifications of substantial risk (Section 8(e)) received (2007 – 2010) (US EPA, ChemView. Accessed April 13, 2017).
Toxic Substances Control Act (TSCA) – Section 4	Provides EPA with authority to issue rules and orders requiring manufacturers (including importers) and processors to test chemical substances and mixtures.	Six submissions from a test rule (Section 4) received in the mid-1990s. (US EPA, ChemView. Accessed April 13, 2017).
Emergency Planning and Community Right-To-Know Act (EPCRA) – Section 313	Requires annual reporting from facilities in specific industry sectors that employ 10 or more full time equivalent employees and that manufacture, process, or otherwise use a TRI-listed chemical in quantities above threshold levels. A facility that meets reporting requirements must submit a reporting form for each chemical for which it triggered reporting, providing data across a variety of categories, including activities and uses of the chemical, releases and other waste management (e.g., quantities recycled, treated, combusted) and pollution prevention activities (under section 6607 of the Pollution Prevention Act). This data includes on-site and off-site data as well as multimedia data (i.e., air, land and water).	NMP is a listed substance subject to reporting requirements under 40 CFR 372.65 effective as of January 1, 1995.
Federal Food, Drug and Cosmetic Act (FFDCA) – Section 408	FFDCA governs the allowable residues of pesticides in food. Section 408 of the FFDCA provides EPA with the authority to set tolerances (rules that establish	NMP is currently approved for use as a solvent and co-solvent inert ingredient in pesticide formulations for both food and

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
	maximum allowable residue limits), or exemptions from the requirement of a tolerance, for all residues of a pesticide (including both active and inert ingredients) that are in or on food. Prior to issuing a tolerance or exemption from tolerance, EPA must determine that the tolerance or exemption is "safe." Sections 408(b) and (c) of the FFDCA define "safe" to mean the Agency has a reasonable certainty that no harm will result from aggregate exposures to the pesticide residue, including all dietary exposure and all other exposure (e.g., non-occupational exposures) for which there is reliable information. Pesticide tolerances or exemptions from tolerance that do not meet the FFDCA safety standard are subject to revocation. In the absence of a tolerance or an exemption from tolerance, a food containing a pesticide residue is considered adulterated and may not be distributed in interstate commerce.	non-food uses and is exempt from the requirements of a tolerance limit (40 CFR Part 180.920).
Clean Air Act (CAA) – Section 111 (b)	Requires EPA to establish new source performance standards (NSPS) for any category of new or modified stationary sources that EPA determines causes, or contributes significantly to, air pollution which may reasonably be anticipated to endanger public health or welfare. The standards are based on the degree of emission limitation achievable through the application of the best system of emission reduction which (considering the cost of achieving reductions and non-air quality health and environmental impacts and energy requirements) EPA determines has been adequately demonstrated.	NMP is subject to Clean Air Act Section 111 Standards of Performance for New Stationary Sources of Air Pollutants for VOC emissions from synthetic organic chemical manufacturing industry distillation operations (40 CFR Part 60, subpart NNN) and reactor processes (40 CFR Part 60, Subpart RRR).

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
Clean Air Act (CAA) – Section 183(e)	Section 183(e) requires EPA to list the categories of consumer and commercial products that account for at least 80 percent of all VOC emissions in areas that violate the National Ambient Air Quality Standards for ozone and to issue standards for these categories that require "best available controls." In lieu of regulations, EPA may issue control techniques guidelines if the guidelines are determined to be substantially as effective as regulations.	NMP is listed under the National Volatile Organic Compound Emission Standards for Aerosol Coatings (40 CFR part 59, subpart E).
Clean Air Act (CAA) – Section 612	Under Section 612 of the Clean Air Act (CAA), EPA's Significant New Alternatives Policy (SNAP) program reviews substitutes for ozone depleting substances within a comparative risk framework. EPA publishes lists of acceptable and unacceptable alternatives. A determination that an alternative is unacceptable, or acceptable only with conditions, is made through rulemaking.	Under EPA's SNAP program, EPA listed NMP as an acceptable substitute for "straight organic solvent cleaning (with terpenes, C620 petroleum hydrocarbons, oxygenated organic solvents such as ketones, esters, alcohols, etc.)" for metals, electronics and precision cleaning and "Oxygenated organic solvents (esters, ethers, alcohols, ketones)" for aerosol solvents (59 FR, March 18, 1994).
Safe Drinking Water Act (SDWA) – Section 1412 (b)	Every 5 years, EPA must publish a list of contaminants (1) that are currently unregulated, (2) that are known or anticipated to occur in public water systems, and (3) which might require regulations under SDWA. EPA must also determine whether to regulate at least five contaminants from the list every 5 years.	NMP was identified on both the Third (2009) and Fourth (2016) Contaminant Candidate Lists (74 FR 51850, October 8, 2009) (81 FR 81099 November 17, 2016).
Other Federal Regulations		
Occupational Safety and Health Act (OSHA)	Requires employers to provide their workers with a place of employment free from recognized hazards to safety and health, such as exposure to toxic chemicals, excessive noise levels, mechanical dangers, heat or cold stress, or unsanitary conditions.	OSHA has not established a PEL for NMP.

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
	Under the Act, OSHA can issue occupational safety and health standards including such provisions as Permissible Exposure Limits (PELs), exposure monitoring, engineering and administrative control measures and respiratory protection.	
Federal Food, Drug and Cosmetic Act (FFDCA)	Provides the U.S Food and Drug Administration (FDA) with authority to oversee the safety of food, drugs and cosmetics.	Food and Drug Administration identifies NMP as an "Indirect Additive Used in Food Contact Substances" specifically as: 1) an adjuvant substance in the preparation of slimicides (21 CFR 176.300), 2) an adjuvant substance in the production of polysulfone resin authorized for use as articles intended for use in contact with food (21 CFR 177.1655) and 3) a residual solvent in polyetherone sulfone resins authorized as articles for repeated use in contact with food (21 CFR 177.2440). FDA also identifies NMP as a Class 2 solvent, namely a solvent that "should be limited in pharmaceutical products because of their inherent toxicity." FDA established a Permissible Daily Exposure (PDE) for NMP of 5.3 mg/day with a concentration limit of 530 ppm. FDA's Center for Veterinary Medicine developed a method in 2011 for detection of the residues of NMP in edible tissues of cattle (21 CFR 500.1410)

7493

A.2 State Laws and Regulations

Table_Apx A-2. State Laws and Regulations

State Actions	Description of Action
State Air Regulations	New Hampshire (Env-A 1400: Regulated Toxic Air Pollutants) lists NMP as a regulated toxic air pollutant. Vermont (Vermont Air Pollution Control Regulations, 5261) lists NMP as a hazardous air contaminant.
Chemicals of Concern to Children	Several states have adopted reporting laws for chemicals in children's products that include NMP including Oregon (OAR 333-016-2000), Vermont (18 V.S.A. sections 1771 to 1779) and Washington state (WAC 173-334-130). Minnesota has listed NMP as a chemical of concern to children (Minnesota Statutes 116.9401 to 116.9407).
State Permissible Exposure Limits	California PEL is 1 ppm as an 8hr-time-weighted average (TWA), along with a skin notation (Cal Code Regs, title 8, section 5155).
State Right-to-Know Acts	Massachusetts (454 CMR 21.00), New Jersey (42 N.J.R. 1709(a)) and Pennsylvania (Chapter 323. Hazardous Substance List).
Other	In California, NMP is listed on Proposition 65 (Cal. Code Regs. title 27, section 27001) due to reproductive toxicity. California OEHHA lists a Maximum Allowable Dose Level (MADL) for inhalation exposure = 3,200 µg/day MADL for dermal exposure = 17,000 µg/day. The California Department of Toxic Substances Control (DTSC) Safer Consumer Products Program lists NMP as a Candidate Chemical for development toxicity and reproductive toxicity. In addition, DTSC is moving to address paint strippers containing NMP and specifically cautioned against replacing methylene chloride with NMP. In August 2018 California Department of Toxic Substances Control (DTSC) Safer Consumer Products program proposed to list Paint and Varnish Strippers and Graffiti Removers Containing NMP as a priority product citing (1) potential for human and other organism exposure to NMP in paint and varnish strippers and graffiti removers; and (2) the exposure has the potential to contribute to or cause significant or widespread adverse impacts. DTSC published a Product-Chemical Profile for Paint and Varnish Strippers and Graffiti Removers Containing NMP to support the listing. California Department of Public Health's Hazard Evaluation System and Information Service (HESIS) issued a Health Hazard Advisory on NMP in 2006 and updated the Advisory in June 2014. The Advisory is aimed at workers and employers at sites where NMP is used.

A.3 International Laws and Regulations

Table_Apx A-3. Regulatory Actions by Other Governments and Tribes

Country/Organization	Requirements and Restrictions
European Union	In 2011, NMP was listed on the Candidate list as a Substance of Very High Concern (SVHC) under regulation (EC) No 1907/2006 - REACH (Registration, Evaluation, Authorization and Restriction of Chemicals). In March 2017, NMP was included in the public consultation of chemicals recommended for inclusion in Annex XIV of the European Chemicals Agency (ECHA) under Annex (Authorisation list) of regulation (EC) No 1907/2006 - REACH (Registration, Evaluation, Authorization and Restriction of Chemicals). In 2013, the Netherlands submitted a proposal under REACH to restrict manufacturing and all industrial and professional uses of NMP where workers' exposure exceeds a level specified in the restriction (European Chemicals Agency (ECHA) database. Accessed April 18, 2017). On April 18, 2018, the European Union added NMP to REACH Annex XVII, the restricted substances list. The action specifies three conditions of restriction. The conditions are: 1) NMP shall not be placed on the market as a substance on its own or in mixtures in concentrations greater than 0.3% after May 9, 2020, unless manufacturers, importers and downstream users have included chemical safety reports and safety data sheets with Derived No-Effect Levels (DNELs) relating to workers' exposures of 14,4 mg/m^3 for exposure by inhalation and 4,8 mg/kg/day for dermal exposure; 2) NMP shall not be manufactured, or used, as a substance on its own or in mixtures in a concentration equal to or greater than 0.3% after May 9, 2020 unless manufacturers and downstream users take the appropriate risk management measures and provide the appropriate operational conditions to ensure that exposure of workers is below the DNELs specified above: and 3) the restrictions above shall apply from May 9, 2024 to placing on the market for use, or use, as a solvent or reactant in the process of coating wires.

Country/Organization	Requirements and Restrictions
Australia	NMP was assessed under Human Health Tier III of the Inventory Multi-tiered Assessment and Prioritisation (IMAP) (National Industrial Chemicals Notification and Assessment Scheme, NICNAS, 2017, Human Health Tier III assessment for 2-Pyrrolidinone, 1methyl-. Accessed April,18 2017).
Japan	NMP is regulated in Japan under the following legislation: • Act on the Evaluation of Chemical Substances and Regulation of their Manufacture, etc. (Chemical Substances Control Law) • Industrial Safety and Health Act (National Institute of Technology and Evaluation (NITE) Chemical Risk Information Platform (CHIRP). Accessed April 18, 2017).
European Union and Australia, Austria, Belgium, Canada (Ontario), Denmark, Finland, France, Germany, Ireland, Italy, Latvia, New Zealand, Poland, Spain, Sweden, Switzerland, The Netherlands, Turkey and the United Kingdom.	Occupational exposure limits for NMP (GESTIS International limit values for chemical agents (Occupational exposure limits, OELs) database. Accessed April 18, 2017).

7501

Appendix B LIST OF SUPPLEMENTAL DOCUMENTS

1. Associated Systematic Review Data Quality Evaluation and Data Extraction Documents – Provides additional detail and information on individual study or data evaluations and data extractions including criteria and scoring results.
    a. *Risk Evaluation for N-Methylpyrrolidone (NMP), Systematic Review Supplemental File: Data Quality Evaluation of Environmental Fate and Transport Studies. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019i)
    b. *Risk Evaluation for N-Methylpyrrolidone (NMP), Systematic Review Supplemental File: Data Quality Evaluation of Physical Chemical Properties Studies. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019a)
    c. *Risk Evaluation for N-Methylpyrrolidone (NMP), Systematic Review Supplemental File: Data Quality Evaluation of Environmental Release and Occupational Exposure Data. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019k)
    d. *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) Systematic Review Supplemental File: Data Quality Evaluation of Environmental Release and Occupational Exposure Data- Common Sources. Docket EPA-HQ-OPPT-2019-0236.* (U.S. EPA, 2019l)
    e. *Risk Evaluation for N-Methylpyrrolidone (NMP), Systematic Review Supplemental File: Data Quality Evaluation of Consumer and General Population Exposure Studies. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019h)
    f. *Risk Evaluation for N-Methylpyrrolidone (NMP), Systematic Review Supplemental File: Data Quality Evaluation of Ecological Hazard Studies. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019j)
    g. *Risk Evaluation for N-Methylpyrrolidone (NMP), Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies- Animal Studies. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019m)
    h. *Risk Evaluation for N-Methylpyrrolidone (NMP), Systematic Review Supplemental File: Data Quality Evaluation of Epidemiological Studies. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019n)
    i. *Risk Evaluation for N-Methylpyrrolidone (NMP), Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies.* (U.S. EPA, 2019t)
    j. *Risk Evaluation for N-Methylpyrrolidone (NMP), Systematic Review Supplemental File: Data Extraction Tables for Epidemiological Studies. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019s)

2. *Risk Evaluation for N-Methylpyrrolidone (NMP), Supplemental Information on Occupational Exposure Assessment. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019g) – Provides additional details and information on the occupational exposure assessment including PBPK modeling inputs and air concentration model equations, inputs, and outputs.

3. *Risk Evaluation for N-Methylpyrrolidone (NMP), Supplemental Information on Consumer Exposure Assessment. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019b) – Provides

additional details and information on the consumer exposure assessment, including Consumer Exposure Model (CEM) approach, inputs and sensitivity analysis.

4. *Risk Evaluation for N-Methylpyrrolidone (NMP), Benchmark Dose Modeling Supplemental File. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019f) – Provides additional details and results of the benchmark dose modeling of the human health hazard endpoints.

5. *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Excel File on Occupational Risk Calculations. Docket EPA-HQ-OPPT-2019-0236 (U.S. EPA, 2019q)*

6. *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Consumer Exposure Assessment, Consumer Exposure Model Input Parameters. Docket EPA-HQ-OPPT-2019-0236 (U.S. EPA, 2019c)*

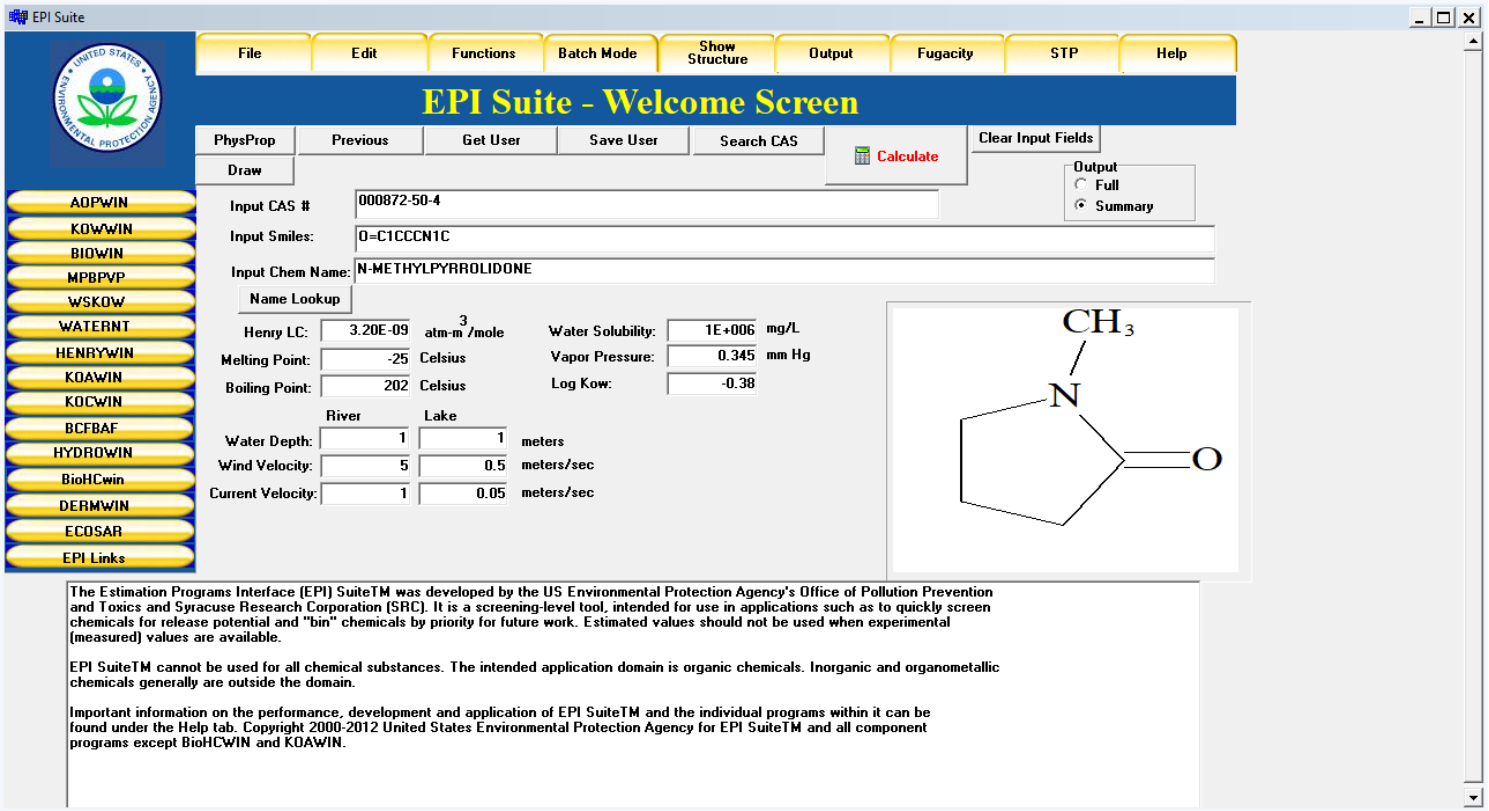
7. *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Consumer Exposure Assessment, Consumer Exposure Model Outputs. Docket EPA-HQ-OPPT-2019-0236 (U.S. EPA, 2019d)*

8. *Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Consumer Exposure Assessment PBPK Model Inputs and Outputs. Docket EPA-HQ-OPPT-2019-0236 (U.S. EPA, 2019e)*

Appendix C FATE AND TRANSPORT

EPI Suite™ Model Inputs

To set up EPI Suite™ for estimating fate properties of NMP, NMP was identified using the "Name Lookup" function. The physical-chemical properties were input based on the values in Table 1-1. EPI Suite™ was run using default settings (i.e., no other parameters were changed or input).



Figure_Apx C-1. EPI Suite Model Inputs for Estimating NMP Fate and Transport Properties

Environmental Fate Study Summary for N-Methyl-2-pyrrolidone (NMP)

7577 **Table_Apx C-1. Biodegradation Study Summary for N-Methylpyrrolidone**

Study Type (year)	Initial Concentration	Inoculum Source	(An)aerobic Status	Duration	Result	Comments	Affiliated Reference	Data Quality Evaluation results of Full Study Report
Water								
Other; Degradation kinetics of NMP in liquid culture under various parameters	≥500 to ≤2000 mg/L	activated sludge, industrial, adapted	aerobic	28h	Biodegradation parameter: half-life: 50%/5.05h	The reviewer agreed with this study's overall quality level.	(Cai et al., 2014)	High
Other; Semi-continuous activated sludge test following ASTM (1975) procedure for biodegradation of synthetic detergents	100 ppm	activated sludge, domestic (adaptation not specified)	aerobic	7d	Biodegradation parameter: percent removal: 95%/7d after 5-day incremental acclimation period (primary biodegradation; complete mineralization not observed)	The reviewer agreed with this study's overall quality level.	(Chow and Ng, 1983)	High
Other; Static die-away test similar to the method recommended by the British Standard Technical Committee of Synthetic Detergents	100 ppm	activated sludge, domestic (adaptation not specified)	aerobic	14d	Biodegradation parameter: COD: 45%/14d; Biodegradation parameter: percent removal: 95%/14d	The reviewer agreed with this study's overall quality level.	(Chow and Ng, 1983)	High
Other; Non-guideline and GLP compliant study.	100 mg/L	Activated sludge from: (1) a municipal wastewater treatment plant in Zlin, Czech Republic and (2) an industrial	aerobic	4d	Biodegradation parameter: oxygen consumption: 50%/4d	The reviewer agreed with this study's overall quality level.	(ECHA, 2017b)	High

Study Type (year)	Initial Concentration	Inoculum Source	(An)aerobic Status	Duration	Result	Comments	Affiliated Reference	Data Quality Evaluation results of Full Study Report
		WTP in Slovenska Lupca, Slovak Republic (pharmaceutical production)						
Other; semi-continuous system	92-200 mg/L	Activated sludge (adaptation not specified) from the Fukashiba Joint Waste Water Treatment Plant	aerobic	24h	Biodegradation parameter: TOC: 92% Biodegradation parameter: percent DOC: 94% Biodegradation parameter: percent removal: >98%	The reviewer agreed with this study's overall quality level. Also reviewed in HERO ID 4140473.	(Matsui et al., 1975)	High
Other; acclimated and unacclimated sludge, static and continuous flow	300-1000 mg/L	acclimated and unacclimated sewage sludge	aerobic	18h hydraulic residence time in continuous cells	Biodegradation parameter: percent removal: 98%	The reviewer agreed with this study's overall quality level. Primary source cited “Lube Solvents No Threat to Waste Treatment” E.H. Rowe and L.F. Tullos, Jr., Hydrocarbon Processing, 59, p. 63-65 (October 1980).	(BASF, 1998)	Medium
Other; not reported	1000 mg/L	activated sludge, non-adapted	aerobic	Adaptation phase of 3.5 days for non-	Biodegradation parameter: COD: >90%	The reviewer agreed with this study's overall quality level.	(BASF, 1998)	Medium

Study Type (year)	Initial Concentration	Inoculum Source	(An)aerobic Status	Duration	Result	Comments	Affiliated Reference	Data Quality Evaluation results of Full Study Report
				acclimated activated sludge		Primary source cited: R. Zahn and H.Z. Wellens Wasser Abwasser Forschung 13, 1 (1980).		
Other; coupled-units	Not reported	activated sludge (adaptation not specified)	not specified	4-12 wks	Biodegradation parameter: DOC: 99%	The reviewer agreed with this study's overall quality level. Primary source cited: A Correlation Study of Biodegradability Determinations with Various Chemicals in Various Tests" P. Gerike and W.K. Fischer Ecotoxicity and Environmental Safety 3, 159 (1979).	(BASF, 1998)	Medium
Other; OECD-screening, test not specified	Not reported	Not reported	not specified	Not reported	Biodegradation parameter: DOC: 99%	The reviewer agreed with this study's overall quality level. Primary source cited: A Correlation Study of Biodegradability Determinations with Various Chemicals in Various Tests" P. Gerike and W.K. Fischer Ecotoxicity and Environmental	(BASF, 1998)	Medium

Study Type (year)	Initial Concentration	Inoculum Source	(An)aerobic Status	Duration	Result	Comments	Affiliated Reference	Data Quality Evaluation results of Full Study Report
						Safety 3, 159 (1979).		
Other; EPA OPPTS 835.3200 (Zahn-Wellens / EMPA Test)	Not reported	Not reported	not specified	28d	Biodegradation parameter: DOC: 98%	The reviewer agreed with this study's overall quality level. Primary source cited: A Correlation Study of Biodegradability Determinations with Various Chemicals in Various Tests" P. Gerike and W.K. Fischer Ecotoxicity and Environmental Safety 3, 159 (1979).	(BASF, 1998)	Medium
Other; EPA OPPTS 835.3110 (Ready Biodegradability)	Not reported	Not reported	not specified	28d	Biodegradation parameter: DOC: 97%	The reviewer agreed with this study's overall quality level. Primary source cited: A Correlation Study of Biodegradability Determinations with Various Chemicals in Various Tests" P. Gerike and W.K. Fischer Ecotoxicity and Environmental Safety 3, 159 (1979).	(BASF, 1998)	Medium

Study Type (year)	Initial Concentration	Inoculum Source	(An)aerobic Status	Duration	Result	Comments	Affiliated Reference	Data Quality Evaluation results of Full Study Report
Other; EPA OPPTS 835.3100 (Aerobic Aquatic Biodegradation)	Not reported	Not reported	not specified	Not reported	Biodegradation parameter: DOC: 95%	The reviewer agreed with this study's overall quality level. The source is a summary document that references "A Correlation Study of Biodegradability Determinations with Various Chemicals in Various Tests" P. Gerike and W.K. Fischer Ecotoxicity and Environmental Safety 3, 159 (1979).	(BASF, 1998)	Medium
OECD Guideline 301 C (Ready Biodegradability: Modified MITI Test (I)); Reported as Japanese MITI test	Not reported in secondary source	activated sludge, domestic (adaptation not specified)	aerobic	28d	Biodegradation parameter: BOD: 73%/28d	The reviewer agreed with this study's overall quality level.	(Toxicology and Regulatory Affairs, 2003)	Medium
Other; Biodegradation of NMP in municipal sewage under static and flow-through conditions and influence of NMP concentrations on non-adapted sludge	≥50 to ≤20000 g/L	activated sludge, adapted	aerobic	≤206h	Biodegradation parameter: theoretical oxygen uptake: 52-93%/≤206h	The reviewer downgraded this study's overall quality rating. They noted: Analytical methods were unclear which limits interpretation of the study results.	(Gomolka and Gomolka, 1981)	Medium
Soil								

Study Type (year)	Initial Concentration	Inoculum Source	(An)aerobic Status	Duration	Result	Comments	Affiliated Reference	Data Quality Evaluation results of Full Study Report
Other; Non-guideline laboratory test	1.7 mg/kg	three types of soils (clay, loam, and sand)	Not specified	3 months	Biodegradation parameter: elimination half-life: 4.0 to 11.5d (soil); 4.0, 8.7, and 11.5d (clay, loam and sand) Biodegradation parameter: percent removal: ≥90%/21d	The reviewer agreed with this study's overall quality level.	(ECHA, 2017a)	Medium

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7579 **Table_Apx C-2. Photolysis Study Summary for N-Methyl-2-pyrrolidone**

Study Type (year)	Wavelength Range	Duration	Result	Comments	Affiliated Reference	Data Quality Evaluation results of Full Study Report
Air						
Other; Rate constants for atmospheric reactions of 1-methyl-2-pyrrolidinone with OH radicals, NO_3 radicals, and O_3 measured and products of the OH radical and NO_3 radical reactions investigated	>300 nm	8-25 min	Photodegradation parameter: indirect photolysis: rate constant: for reaction with OH radicals: (2.15 +/- 0.36)E-11 cm^3 $molecule^{-1}$ s^{-1}; Reaction with NO_3 radicals: (1.26 +/- 0.40)E-13 cm^3 $molecule^{-1}$ s^{-1}	The reviewer agreed with this study's overall quality level.	(Aschmann and Atkinson, 1999)	High

Study Type (year)	Wavelength Range	Duration	Result	Comments	Affiliated Reference	Data Quality Evaluation results of Full Study Report
Other; Photochemical Reaction with OH Radicals			Photodegradation parameter: indirect photolysis: half-life for reaction with OH radicals (QSAR): 17.51 hours	The reviewer agreed with this study's overall quality level.	(ECHA, 2017c)	High
Water						
Photocatalytic decomposition in aqueous solution using light sources of UVA, UVC, and UVLED	254 nm to 385 nm	120 min	Photodegradation parameter: indirect photolysis w/ and w/o catalyst: rate constant: 0.0125 min^{-1} to 0.0454 min^{-1}	Study performed in the presence of catalyst or at wavelengths not relevant to environmental conditions.	(Aliabadi et al., 2012)	Unacceptable

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HERO ID	Reference
3577230	Chow, S. T., Ng, T. L. The Biodegradation Of N-methyl-2-pyrrolidone In Water by Sewage Bacteria. Water Research. 1983. 17:117-118.
1583365	Aliabadi, M., Ghahremani, H., Izadkhah, F., Sagharigar, T. Photocatalytic Degradation of N-methyl-2-pyrrolidone In Aqueous Solutions Using Light Sources of UVA, UVC and UVLED. Fresenius Environmental Bulletin. 2012. 21:2120-2125.
3970767	ECHA. Biodegradation in soil: 1-methyl-2-pyrrolidone. 2017.
3970766	ECHA. Biodegradation in water: screening tests: 1-methyl-2-pyrrolidone. 2017.
3576998	Cai S, hu, Cai T, Liu S, et al. 2014. Biodegradation of N-methylpyrrolidone by Paracoccus sp. NMD-4 and its degradation pathway. International Biodeterioration & Biodegradation 93:70-77. http://doi.org/10.1016/j.ibiod.2014.04.022. http://dx.doi.org/10.1016/j.ibiod.2014.04.022.
1721939	Aschmann, S. M., Atkinson, R Atmospheric chemistry of 1-methyl-2-pyrrolidinone. Atmospheric Environment. 1999. 33:591-599.

HERO ID	Reference
3970781	ECHA. Phototransformation in air: 1-Methyl-2-pyrrolidone. 2017.
3970220	Toxicology Regulatory Affairs. 2-Pyrrolidone. 2003.
3577684	Gomolka, B., Gomolka, E THE EFFECT OF N-METHYLPYRROLIDONE (NMP) ON THE ACTION OF ACTIVATED-SLUDGE. Acta Hydrochimica et Hydrobiologica. 1981. 9:555-572.
4140473	BASF. (1998). N-methyl pyrrolidone biodegradability.

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Appendix D RELEASES TO THE ENVIRONMENT

Systematic Review for Environmental Exposures

During problem formulation, it was determined that the aquatic exposure pathway would not be further analyzed for NMP. The PECO was updated accordingly and all of the "on-topic" studies that entered the process were screened out at Level 3, prior to data evaluation. However, "on-topic" exposure literature for NMP did follow the systematic review process. 132 references were identified as "on-topic" and subjected to an initial title/abstract screen (Level 1) and proceeded to full-text screening (Level 2 and 3). 29 references proceeded to a "Gateway" screen (Level 3), intended to consider alignment with the current PECO. Only 22 references that entered Level 3 moved forward to data evaluation (Level 4).

First-tier Aquatic Exposure Assessment for NMP

EPA used data from EPA's Toxics Release Inventory (TRI) to estimate NMP concentrations released to ambient water by discharging facilities. This "first-tier" exposure assessment was used to derive conservative estimates of NMP surface water concentrations near facilities that reported the highest NMP water releases. EPA identified the top 12 industries reporting the highest NMP water releases and used the reported information to estimate surface water concentrations based on the 2015 TRI data and EPA's Exposure and Fate Assessment Screening Tool, Version 2014. The environmental release data used for this first-tier aquatic exposure assessment and reported in the NMP Problem Formulation can be found in Table_Apx D-1 (U.S. EPA, 2018c).

Table_Apx D-1. Summary of NMP TRI Releases to the Environment in 2015 (lbs)

	Number of Facilities	Air Releases		Water Releases	Land Disposal			Other Releases [b]	Total Releases [c]
		Stack Air Releases	Fugitive Air Releases		Class I Under-ground Injection	RCRA [a] Subtitle C Landfills	All other Land Disposal [b]		
Subtotal		887,309	546,060		3,625,939	93,217	2,737,671		
Total	396	1,433,370		14,092	6,456,827			228,099	8,132,388

Data source: 2015 TRI Data (updated October 2018) (U.S. EPA, 2017f).
[a] RCRA (Resource Conservation and Recovery Act)
[b] Terminology used in these columns may not match the more detailed data element names used in the TRI public data and analysis access points.
[c] These release quantities do include releases due to one-time events not associated with production such as remedial actions or earthquakes.

Surface Water Concentrations

Surface water concentrations were estimated for multiple scenarios using E-FAST 2014, which can be used to estimate site-specific surface water concentrations based on estimated loadings of NMP into receiving water bodies. For TRI, the facilities' reported release quantities can be based on estimates from monitoring data or measurements (i.e., continuous, random, or periodic), mass balance calculations, published or site-specific emission factors, or other approaches such as engineering calculations or best engineering judgment. E-FAST 2014 incorporates stream dilution at the point of release using stream flow distribution data contained within the model. Site-specific stream flow data

are applied using a National Pollutant Discharge Elimination System (NPDES) code. If a specific discharger's NPDES code could not be identified within the E-FAST database, a surrogate site or generic Standard Industrial Classification (SIC) code was applied.

EPA considered multiple scenarios to estimate NMP concentrations in surface water resulting from industrial discharges. Using the 2015 TRI data and EPA's first-tier, Probabilistic Dilution Model (PDM) within the EPA Exposure and Fate Assessment Screening Tool (E-FAST), facilities reporting the largest releases of NMP were modeled based on the assumption of 12 or 250 days of release. The 12-day release scenario represents an acute exposure scenario wherein periodic maintenance and cleaning activities could result in monthly releases. The 250-day release scenario represents a chronic exposure scenario in which standard operations may result in continuous, or more protracted discharges of NMP. Six facilities reported direct discharges of NMP to surface waters and seven facilities reported transfer of NMP to a municipal treatment facility also known as a Publicly Owned Treatment Works (POTW) facility for treatment and discharge into surface waters.

EPA did not identify water monitoring data for NMP during its review of the national surface water monitoring database. The 2015 TRI data on direct and indirect environmental releases were used to estimate NMP concentrations in surface water. Direct releases represent environmental releases of NMP that are discharged directly from a facility into a receiving water body (after treatment), whereas indirect releases are releases from the POTW where the facility has transferred NMP. The POTW releases are discharges to surface water that occur following treatment. EPA used an estimated removal rate of 92% in estimating NMP remaining in treated wastewater from indirect POTW discharges. Because TRI reported facility direct releases are the amounts at discharge, EPA estimates of surface water concentrations did not account for any additional treatment by an onsite system. The predicted surface water concentrations presented in below in Table_Apx D-2 are associated with a low flow – 7Q10, which is an annual minimum seven-day average stream flow over a ten-year recurrence interval. No post-release degradation or removal mechanisms (e.g., hydrolysis, aerobic degradation, photolysis, volatilization) are applied in the calculation of the modeled surface water concentrations.

For the facility transferring NMP waste to the POTW in Pensacola, Florida, the POTW diverts 85% of its treated wastewater for reuse in other industrial facilities as process water. Only 15% of the treated wastewater is discharged into the receiving water of Perdido Bay. EPA therefore, estimated the NMP stream/receiving water concentration based on 15% of total NMP-containing treated wastewater discharged.

To capture "high-end" surface water concentrations, EPA compiled the release data for six facilities that reported the largest NMP direct water releases. This represented > 99% of the total volume of NMP

Table_Apx D-2. Estimated NMP Surface Water Concentrations[a]

Top Facility Discharges (2015)		Onsite NMP Wastewater Releases[a] (lbs/yr)	NMP Transfers to Offsite POTW[a] (lbs/yr)	PDM; input loadings (kg/site/day)		PDM; stream NMP concentrations	
Facility Location	State			12 day scenario	250 day scenario	12 day (µg/L)	250 day (µg/L)
Wilmington	NC	8,987	0	339.71	16.31	224.00	10.75
Richmond	VA	4,602	0	173.96	8.35	119.70	5.75

Essex Junction	VT	451	0	17.05	0.82	44.49	2.14
Bradford	PA	26.83	0	1.01	0.05	8.49	0.4
Fort Wayne	IN	22.1	0	0.84	0.04	5.56	0.27
Wyandotte	MI	2	62.83	0.08	0.00	0.0011	0.14
Westborough	MA		100,606		183		863
Wilmington	MA		533,525		968		60
Pensacola	FL		154,798		281		878[b]
Saint Louis	MO		150,011		272		636
Aloha	OR		170,000		308		499
Hillsboro	OR		510,000		925		1,496

[a] From 2015 Toxics Release Inventory (TRI)
[b] Wastewater influent has undergone pretreatment and is treated again at this POTW.

reported as a direct discharge to surface water during the 2015 TRI reporting period. Since there were many more facilities reporting indirect releases of NMP to surface water, seven of the facilities reporting the largest indirect water releases (representing ~ 11% of the total number of facilities reporting indirect discharges) were compiled. The volume of NMP released from these facilities encompassed more than 68% of the total volume of NMP reported as an indirect discharge to surface water.

The "high-end" surface water concentrations (i.e., those obtained assuming a low stream flow for the receiving water body) from all PDM runs ranged from 1.1E-03 µg/L to 224 µg/L, for the acute (i.e., fewer than 20 days of environmental releases per year) and 0.14 µg/L to 1,496 µg/L chronic exposure scenario (i.e., more than 20 days of environmental releases per year assumed), respectively. The maximum acute scenario concentration was 224 µg/L and the maximum chronic scenario concentration was 1,496 µg/L. Comparing these concentrations with the respective aquatic ecological concentrations of concern of 246 ug/L for acute and 1,768 ug/L for chronic results in no exceedances (see Table 4-1). EPA does not anticipate a concern to aquatic organisms from NMP discharges to surface waters.

EPA did not evaluate the human health concerns from NMP releases to surface water since drinking water, the main source of NMP exposure from surface water, is regulated via the EPA Office of Water Contaminant Candidate List (CCL 3).

Appendix E OCCUPATIONAL EXPOSURES

Section E.1 contains information gathered by EPA in support of understanding glove use for pure NMP and for using NMP-containing formulations.

E.1 Information on Gloves for Pure NMP and for Formulations containing NMP

Section E.1.1 contains information gathered by EPA in support of understanding glove use for pure NMP and for paint and coatings removal using NMP formulations. Section E.1.2 contains information on gloves and respirators from Safety Data Sheets (SDS) for NMP and NMP-containing Products.

E.1.1 Specifications for Gloves for Pure NMP and in Paint and Coating Removal Formulations containing NMP

Section E.1.1 contains information gathered by EPA in support of understanding glove use for pure NMP and for paint and coatings removal using NMP formulations (EPA-HQ-OPPT-2016-0231-0200). This information may be generally useful for a broader range of uses of NMP and is presented for illustrative purposes.

Summary on Suitable Gloves for Pure NMP and in Formulations

For scenarios where gloves can provide protection to achieve benchmark MOEs, gloves should be tested to determine whether they are protective against the specific formulation of the product that contains NMP. Several studies found in the literature indicate that the best types of glove material to protect against dermal exposure to pure NMP are Silver Shield, Butyl Rubber and Ansell Barrier laminate film. The next best types of glove among those studied to use for NMP exposure would be Neoprene and Natural Rubber/Latex. Among the studies, Silver Shield provided the best protection against NMP, whether it was in pure form or part of a tested formulation. Detailed information on these and other glove types which were evaluated for their permeation characteristics against NMP are provided below. The cited studies' results may be a good starting point for determining glove types to consider for glove testing.

Gloves for Pure NMP

There are many factors that determine proper chemical-resistant glove selection. In addition to the specific chemical(s) utilized, the most important factors include duration, frequency, and adversity of chemical exposure. The degree of dexterity required for the task and associated physical stress to the glove are also significant considerations. The manner in which employees are able to doff the various glove types to best prevent skin contamination is also important but sometimes overlooked.

Generally, dermal exposures to the solvents in paint and coating removal formulations may be assumed to be frequent or lengthy and may result in significant exposure. These assumptions affect the proper choice of glove type and errs on the side of caution, which is advised for any personal protective

equipment (PPE) decision since PPE is the last line of defense against exposure in an industrial hygienist's hierarchy of controls.

Table_Apx E-1 below summarizes commonly used industrial hygiene literature (e.g., glove selection guides, manufacturer publications, etc.) and capture the highest rated glove types from each reference. Consideration of all factors (breakthrough time, qualitative indicator (QI), and other issues raised in the comments field) allow an overall determination of effectiveness.

Table_Apx E-1. Glove Types Evaluated for Pure N-Methylpyrrolidone (NMP)

Reference	Glove type	Breakthrough Time	Qualitative Indicator	Comments
1	Ansell Barrier (Laminate Film) Glove	>480 mins	Very well suited	Degradation rate: Good-Excellent. Permeation rate: Excellent
	Natural Rubber	75 mins	Very well suited	Degradation rate: Excellent. Permeation rate: Very Good
	Butyl	>480 mins	Very well suited	Degradation rate: Excellent
2	Neoprene over Natural Rubber (Best Chem Master)	>480 mins	Safest, best selection	Highest rating attainable
	Butyl	>480 mins	Safest, best selection	Highest rating attainable
	Neoprene (Chloroflex)	>480 mins	Safest, best selection	Highest rating attainable
4	Butyl	8 hrs	Good for total immersion	Degradation rate: Excellent
	Natural Rubber	1.26 hrs	Good for accidental splash protection and intermittent contact	Degradation rate: Fair
	Nitrile	1.45 hrs	Good for accidental splash protection and intermittent contact	Degradation rate: Fair
8	Neoprene	226 mins	Used for high chemical exposure	Specific glove evaluated is Chem Ply N-440
	Natural Latex / Neoprene / Nitrile	50 mins	Used for repeated chemical contact	Specific glove evaluated is Trionic O-240
10	Silver Shield (North)	Not Provided	Recommended	Silver Shield and Butyl rubber gloves are the only two glove types recommended by this source
	Butyl	Not Provided	Recommended	

Based on the information from Table_Apx E-1, the three best types of glove material to protect against pure NMP dermal exposure are Silver Shield, Butyl Rubber and Ansell Barrier laminate film. The next best types of glove to use for pure NMP exposure would be Neoprene and Natural Rubber/Latex. As mentioned previously, Silver Shield gloves do not provide acceptable dexterity for most workers, so

they are commonly worn as a base glove with a tighter-fitting glove (e.g. latex) over the top. Alternatively, Butyl Rubber or Ansell Barrier laminate film gloves could be worn and would provide significant protection.

Key Points and Examples for Paint and Coating Removal Formulations

The U.S. EPA's Safety, Health and Environmental Management Division's (SHEMD) Guideline 44 (Personal Protective Equipment) states that when working with mixtures and formulated products, the chemical component with the shortest break-through time must be considered when determining the appropriate glove type for protection against chemical hazards unless specific test data are available (SHEMD 2004). Additionally, an industrial hygienist will consider the formulation's chemical properties, including the highest hazard component of the formulation, and whether individual components produce synergistic degradation effects. Typically, specific test data for formulations are not available and best judgment, based on these considerations provides the basis for glove type selection. However, in this case there are a few publications that specifically address glove types for use with methylene chloride and NMP as part of paint and coating removal formulations.

In early 2002, an article entitled "A Comparative Analysis of Glove Permeation Resistance to Paint Stripping Formulations" (Stull et al., 2002) specifically examined which glove types provide the best protection to users of commercial paint and coating removal products. Twenty different glove types were evaluated for degradation and resistance to permeation under continuous and/or intermittent contact with seven different paint and coating removal formulations in a multiple-phase experiment. Paint and coating removal formulations included some that were methylene chloride-based and others that were NMP-based. The study found that gloves made of Plastic Laminate (e.g. Silver Shield) resisted permeation by the majority of paint and coating removal while Butyl Rubber provided the next best level of permeation resistance against the majority of formulations. However, Butyl Rubber gloves did show rapid permeation for methylene chloride-based formulations and would not be recommended for methylene chloride. It should be noted that PVA gloves, shown to be effective against pure methylene chloride, were not evaluated. Interestingly, more glove types resisted permeation of NMP-based formulations than conventional solvent-based products such as methylene chloride. The results showed that relatively small-molecule, volatile, chemical-based solvents cause somewhat more degradation and considerably more permeation of glove types as compared with NMP-based formulations against the same gloves. Key conclusions include the following: "However, paint stripper formulations represent varying multichemical mixtures and, ultimately, commercial paint strippers must be individually evaluated for permeation resistance against selected gloves" (Stull et al., 2002), and, "because of several potential synergistic effects well established in the literature and in this study for mixture permeation, it is highly recommended that glove selection decisions be based on testing of the commercial paint stripper against the specific glove in question" (Stull et al., 2002).

Another study from in 2007 entitled "Protective Glove Selection for Workers using NMP-Containing Products: Graffiti Removal" essentially came to the same conclusion; of the gloves studied Silver Shield gloves provide the best protection against NMP-based paint and coating removal formulations (Health and Safety Laboratory, 2007). The study states that "Butyl gloves, used with caution would be a second choice" (Health and Safety Laboratory, 2007). The increased dexterity and robustness of Butyl gloves were noted as an advantage of Butyl over Silver Shield. Key recommendations include that gloves

should be "tested against all relevant chemical formulations as a matter of routine in order to inform glove selection" (Health and Safety Laboratory, 2007) and "assumptions of glove choice based on the use of model compounds or similar formulations should be made with extreme caution (Health and Safety Laboratory, 2007)." Additionally, Crook recommended that "The BS EN 374-3 continuous contact test and its successors should remain the benchmark for chemically protective glove type decisions" (Health and Safety Laboratory, 2007).

In summary, these studies indicate that glove permeation continuous contact testing of each formulation is necessary to provide proper protection. These studies' results may be a good starting point for determining glove types to consider for permeation testing. The studies found that among gloves tested Silver Shield provide the best protection against both methylene chloride and NMP, whether they are in pure form or as part of a tested formulation. The best alternative for protection against methylene chloride would be PVA gloves, while the best alternative for NMP protection would be Butyl Rubber gloves. A more task-specific decision on appropriate glove type selection could be made through employee interviews and observation of tasks using methylene chloride- or NMP-containing products.

E.1.2 Information on Gloves and Respirators from Safety Data Sheets (SDS) for NMP and NMP-containing Products

EPA reviewed safety data sheets (SDSs) for neat NMP and products containing NMP for information on glove and respiratory protection. Specifically, EPA reviewed SDSs for each occupational exposure scenario assessed in Section 2.4.1.2. EPA compiled the recommended glove materials and respiratory protection for each occupational exposure scenario from the reviewed SDSs (total of 21 SDSs were reviewed) in Table_Apx E-2. For neat NMP and NMP-containing products, the SDSs recommend a variety of glove materials, including butyl rubber (8 SDSs), nitrile rubber (9 SDSs), neoprene (8 SDSs), natural rubber (4 SDSs), polyvinyl chloride (PVC) (4 SDSs), latex (2 SDSs), and Teflon (1 SDS). Note that many of the reviewed SDSs included multiple glove material recommendations. Almost half of the reviewed SDSs indicated that respiratory protection was not needed under normal conditions with adequate ventilation, unless exposure limits are exceeded or workers experience irritation or other symptoms (10 of 21 SDSs). Three SDSs recommend the use of respirators with organic vapor cartridges. Four SDSs recommend the use of particulate filters in instances where mist or dusts may form while using the NMP-containing product. Four SDSs recommend the use of a self-contained breathing apparatus (SCBA) for emergency situations, such as spills, that can create intensive or prolonged exposure. Note that many of the reviewed SDSs included respiratory protection recommendations, based on the exposure scenario (i.e., normal use, emergency, potential for mist or dust).

Table_Apx E-2. Recommended Glove Materials and Respiratory Protection for NMP and NMP-Containing Products from Safety Data Sheets

Applicable Occupational Exposure Scenario	Material, NMP wt.%	Recommended Glove Material	Recommended Respiratory Protection	Source
Manufacturing; Repackaging; Chemical Processing, Excluding Formulation; Incorporation into a Formulation, Mixture or Reaction Product; Laboratory Use	Neat, 99-100%	Butyl rubber	No specific respirator recommended. SDS indicates to use an approved respirator if exposure limits are exceeded.	(Tedia, 2011)
Manufacturing; Repackaging; Chemical Processing, Excluding Formulation; Incorporation into a Formulation, Mixture or Reaction Product; Laboratory Use	Neat, 99%	Nitrile rubber, neoprene, butyl rubber	Industrial uses: Organic gases and vapors filter Type A Brown conforming to EN14387. Laboratory Use: Half mask, Valve filtering; or, Half mask, plus filter	(Thermo Fisher, 2019)
Application of Paints, Coatings, Adhesives and Sealants	Mixture, >85%	Butyl rubber or Teflon gloves	If vapors or mists are generated, wear a NIOSH/MSHA approved organic vapor/mist respirator or an air supplied respirator as appropriate. Use only self-contained breathing apparatus for emergencies.	(AZEK, 2015)
Application of Paints, Coatings, Adhesives and Sealants	Mixture, <1%	Polymer laminate; nitrile gloves may be worn over polymer laminate gloves to improve dexterity	Half facepiece or full facepiece air-purifying respirator suitable for organic vapors and particulates.	(3M, 2018)
Application of Paints, Coatings, Adhesives and Sealants	Mixture, <1%	Nitrile gloves	No specific respirator recommended. SDS indicates to use an	(Ball, 2013)

Applicable Occupational Exposure Scenario	Material, NMP wt.%	Recommended Glove Material	Recommended Respiratory Protection	Source
			approved respirator if exposure limits are exceeded.	
Printing and Writing	Mixture, >15%	Neoprene, butyl, or nitrile rubber	No specific respirator recommended. SDS indicates to use an approved respirator if exposure limits are exceeded.	(Voxel8, 2015)
Printing and Writing	Mixture, 0-5%	Neoprene, butyl, or nitrile rubber gloves with cuffs	No specific respirator recommended. SDS indicates to use an approved respirator if exposure limits are exceeded.	(Novacentrix, 2016)
Metal Finishing [a]	Mixture, 1-5%	Rubber gloves	No specific respirator recommended. SDS indicates to use an approved respirator if exposure limits are exceeded.	(U.S. Chemical, 2012)
Metal Finishing [a]; Automotive Car Servicing (aerosol use) [b]	Mixture, unspecified NMP concentration	Nitrile or polyvinyl chloride (PVC) gloves	No specific respirator recommended. SDS indicates to use an approved respirator if exposure limits are exceeded.	(Simoniz, 2012)
Removal of Paints, Coatings, Adhesives, and Sealants	Mixture, 20-30%	Butyl Rubber	Half facepiece or full facepiece air-purifying respirator suitable for organic vapors.	(3M, 2014)
Removal of Paints, Coatings, Adhesives, and Sealants	Mixture, 41%	Use gloves chemically resistant to this material (Neoprene, Nitrile, PVC)	No specific respirator recommended. SDS indicates to use an	(TLS, 2016)

Applicable Occupational Exposure Scenario	Material, NMP wt.%	Recommended Glove Material	Recommended Respiratory Protection	Source
			approved respirator if exposure limits are exceeded.	
Cleaning	Mixture, 90-95%	PVC-lined, latex, or Nitrile gloves	Normal use: Use NIOSH approved respiratory protection. Emergency: Self-contained breathing apparatus, air-line respirator, full-face respirator	(Crest, 2011)
Cleaning	Mixture, 1-5%	Natural Latex or Rubber	Normal use: not required. Emergency: A2P2 - Combo filter: gas filter type A with medium capacity and a class P2 particle filter.	(Prestige, 2010)
Automotive Car Servicing (aerosol use) [b]	Mixture, 30-40%	Neoprene	No specific respirator recommended. SDS indicates to use an approved respirator if exposure limits are exceeded.	(Slide, 2018)
Electronics Manufacturing	Mixture, unspecified NMP concentration	Butyl rubber	In case of low exposure, use cartridge respirator. In case of intensive or longer exposure, use self-contained breathing apparatus.	(MicroChem, 2012)
Electronics Manufacturing	Mixture, 0-1%	Neoprene or natural rubber gloves if handling an open or leaking battery	Not necessary under normal conditions.	(Lenmar, 2014)

Applicable Occupational Exposure Scenario	Material, NMP wt.%	Recommended Glove Material	Recommended Respiratory Protection	Source
Soldering	Mixture, 1-3%	Nitrile rubber or natural rubber	When ventilation is not sufficient to remove fumes from the breathing zone, a safety approved respirator or self-contained breathing apparatus should be worn.	(Kester, 2017)
Fertilizer Application	Mixture, <1%	Neoprene gloves	Wear air supplied respiratory protection if exposure concentrations are unknown. In case of inadequate ventilation or risk of inhalation of dust, use suitable respiratory equipment with particle filter.	(Koch, 2011)
Fertilizer Application	Mixture, <10%	Chemical resistant gloves	Wear air supplied respiratory protection if exposure concentrations are unknown. In case of inadequate ventilation or risk of inhalation of mist, use suitable respiratory equipment with particle filter.	(Koch, 2018)
Wood Preservatives	Mixture, <1%	Chemical-resistant gloves (such as barrier laminate, butyl rubber, nitrile rubber, neoprene rubber, polyvinyl chloride, vitro)	No specific respirator recommended. SDS indicates to use an approved respirator if exposure limits are exceeded.	(Osmose, 2015)

Applicable Occupational Exposure Scenario	Material, NMP wt.%	Recommended Glove Material	Recommended Respiratory Protection	Source
Recycling and Disposal [c]	Reclaimed neat NMP, 99-100%	chemical resistant gloves	Use NIOSH-certified, air-purifying respirators with organic vapor cartridges when concentration of vapor or mist exceeds applicable exposure limits. Protection provided by air-purifying respirators is limited.	(Safety-Kleen, 2015)

[a] These products are recommended for use on metal parts, but EPA does not know the extent to which these products may be used within the six operations listed under metal finishing at 40 CFR 433.10.
[b] These SDSs are for aerosol cleaning products. EPA does not know the extent to which these products are used in the automotive service industry.
[c] Saftey-Kleen is a waste management company; however, this SDS does not explicitly state that the NMP has been reclaimed.

7817

Appendix F CONSUMER EXPOSURES

F.1 Overview of the E-FAST/CEM Model

The Exposure and Fate Assessment Screening Tool Version 2 (E-FAST2) Consumer Exposure Module (CEM) was selected for the consumer exposure modeling as the most appropriate model to use due to the lack of available emissions and monitoring data for NMP uses other than paint removers under consideration. Moreover, EPA did not have the input parameter data from specific NMP product chamber studies required to run more complex indoor air models for the consumer products under the scope of this assessment. CEM uses high-end input parameters/assumptions to generate conservative, upper-bound inhalation exposure estimates for aerosol spray products. The advantages of CEM are the following:

1. CEM model has been peer-reviewed.
2. CEM accommodates the inputs available for the products containing NMP in the indoor air model.
3. CEM uses the same calculation engine to compute indoor air concentrations from a source as the Multi-Chamber Concentration and Exposure Model (MCCEM) but does not require measured emission values (e.g. chamber studies).

Modeling Air Concentrations and Inhalation Exposure

The model used a two-zone representation of a house to calculate the potential acute dose rate (mg/kg-bw/day) of NMP for users and non-users. Zone 1 represents the area where the consumer is using the product, whereas Zone 2 represents the remainder of the house. Zone 2 can be used for modeling passive exposure to non-users in the home (bystanders), such as children and the elderly.

The general steps of the calculation engine within the CEM model included:

1. Introduction of the chemical (i.e., NMP) into the room of use (Zone 1),
2. Transfer of the chemical to the rest of the house (Zone 2) due to exchange of air between the different rooms,
3. Exchange of the house air with outdoor air and,
4. Summation of the exposure doses as the modeled occupant moves about the house

The chemical of concern (i.e., NMP) enters the room air through two pathways: (1) overspray of the product and (2) evaporation from a thin film. Six percent (6%) of the product was assumed to become instantly aerosolized (i.e. product overspray) and was available for inhalation.
The CEM model uses data from the evaporation of a chemical film to calculate the rate of the mass evaporating from the application surface covered during product use (DTIC, 1981). The model assumes air exchanges from the room of use (Zone 1) and the rest of the house (Zone 2) according to interzonal flow. The model also allows air exchange from the house (Zone 1 & 2) with the outdoor air.
EPA used the default activity pattern in CEM based on the occupant being present in the home for most of the day. As the occupants moved around the house in the model, the NMP air concentration would vary. The exposure to the calculated air concentrations were summed using CEM to estimate a potential 24-hr dose.

The potential inhalation acute dose rates (ADR pot) are computed iteratively by calculating the peak concentrations for each simulated 10-second interval and then summing the doses over 24 hrs. These calculations take into consideration the chemical emission rate over time, the volume of the house and the zone of use, the air exchange rate and interzonal airflow rate, the exposed individual's locations, body weights and inhalation rates during and after the product use. The reader is referred to the EPA's E-FAST2 website (http://www.epa.gov/tsca-screening-tools/e-fast-exposure-and-fate-assessment-screening-tool-version-2014) to obtain additional information about the model, including the model documentation and algorithms used (U.S. EPA, 2017a).

Thus, the user's exposure to NMP depends on their activity pattern (i.e., how much time using the product, as well as the time in the room of use or in the rest of the house) as to the concentration of NMP in the air within each of these areas. Based on the varying air concentrations estimated by the CEM model over a 24-hour period, EPA then used the PBPK model to estimate internal dose of NMP from inhalation.
Chronic exposure assessments were not performed for any of the consumer COUs because the frequency of product used is unlikely to present a concern for chronic exposure.

Modeling Dermal Exposure
Since consumers do not always wear gloves when using consumer products, EPA modeled dermal exposures for all NMP-containing products. Though CEM can estimate dermal exposures using a chemical permeability coefficient, EPA used the PBPK model to estimate the internal dose of NMP as it is absorbed through the skin both from direct contact of the liquid product and through absorption of vapor through skin. The PBPK model thus, estimated the total internal dose of NMP through combined routes of exposure: inhalation, dermal and vapor through skin and was used to estimate exposures in the Paint Remover Risk Assessment.

United States Environmental Protection Agency

July 2016
Office of Chemical Safety and Pollution Prevention

Supplemental Consumer Exposure and Risk Estimation Technical Report for NMP in Paint and Coating Removal [RIN 2070-AK07]

July 2016

1. Introduction

EPA performed this technical analysis of consumer exposure scenarios for the use of N-methylpyrrolidone (NMP) in paint and coating removal. Consistent with its final TSCA Work Plan Chemical Risk Assessment for NMP (EPA, 2015), this analysis adds additional exposure scenarios associated with the use of NMP in consumer paint and coating removal.

2. Executive Summary

In 2015, EPA completed a risk assessment for NMP in paint and coating removal (EPA, 2015)[7]. The NMP risk assessment found risks of concern for occupational use and certain consumer uses of NMP in paint and coating removal. EPA conducted exposure modeling and risk analyses to investigate additional exposure parameters to those included in the NMP risk assessment. .

The NMP risk assessment evaluated risks based on emissions data from a brush-applied product. This supplemental analysis used the same modeling methods to evaluate exposures and estimate risks from larger projects. This additional exposure modeling describes the same product type (paint and coating removal product) as in the NMP risk assessment, but with extended application times, increased product use and altered user behavior.

The expanded consumer exposure modeling used the Multi-Chamber Concentration and Exposure Model (MCCEM) (EPA, 2010), the same model used in the NMP risk assessment. MCCEM was used to estimate 24-hr indoor air concentrations of NMP (i.e., acute exposure) for the additional consumer exposure modeling scenarios described here. These air concentrations were calculated for both users[8] and bystanders[9] of paint and coating removal products containing NMP in a residential setting. Generally, the modeling reported in this document adopted many of the input parameters and assumptions described in the NMP risk assessment, with the exception of those variations necessary to evaluate additional consumer exposure scenarios.

The risk calculations used physiologically-based pharmacokinetic (PBPK) modeling to incorporate both the airborne exposure, calculated in this document, and the dermal exposures resulting from product use. This is the same methodology as was applied in the NMP risk assessment. The results of the risk calculations are discussed in the section 6 of this document. As expected, the larger projects modeled in this analysis resulted in larger indoor air concentrations and longer dermal exposures and based on those higher exposures, concerns for developmental effects were found for some of the additional exposure scenarios evaluated.

[7] EPA (U.S. Environmental Protection Agency). 2015. *TSCA Work Plan Chemical Risk Assessment, N-Methylpyrrolidone: Paint Stripper Use, CASRN: 872-50-4.* Office of Pollution Prevention and Toxics, Washington, DC. https://www.epa.gov/sites/production/files/2015-11/documents/nmp_ra_3_23_15_final.pdf

[8] Users are directly involved of the application of the painter remover to a painted surface

[9] Non-users are other inhabitants of the home that spend most of their day inside but do not enter the room where the paint remover is used.

3. Background of Consumer Exposure Analysis for Paint and Coating Removal Products Presented in EPA's NMP Risk Assessment

The assessment of consumer use of paint and coating removal products in the NMP risk assessment used information from products containing NMP and surveys of users to estimate concentrations of NMP in indoor air due to product use (EPA, 2015). The parameters and their origins are explained in the NMP risk assessment, specifically in Section 2.2 and Appendix E (EPA, 2015).

In the NMP risk assessment and in this supplemental analysis, EPA used MCCEM to estimate NMP inhalation exposures for the consumer use scenarios (EPA, 2010). This modeling approach was selected because emission data were available from chamber studies for a product containing NMP. The model used a multi-zone representation of a house to calculate the NMP exposure levels for consumers (users) and bystanders (non-users). In this model, the room in which the product was used was represented by one or two zones, and the rest of the house (ROH) volume represents another zone. The user was assumed to spend time in the room of use on the day of use, whereas the non-user was modeled as spending the day in the rest of the house or outside (EPA, 2015).

The modeling approach integrated assumptions and input parameters about the chemical emission rate over time, the volume of the house and the room of use, the air exchange rate and interzonal airflow rate. The model also considered the exposed individual's location during and after product use (EPA, 2010).

MCCEM was used to calculate minute by minute air concentrations based on the behavior patterns assumed in the model. A description of the original modeled inputs and their sources as well as a description of how MCCEM was implemented for paint removers is also in the NMP risk assessment (EPA, 2015).

4. Additional Exposure Analysis for Consumer Paint and Coating Removal

Modeling using the same methodology was conducted for additional consumer exposure scenarios to aid in understanding how exposures and risk might change by varying certain user behaviors or product application techniques. The same consumer exposure model, MCCEM, used for the NMP risk assessment was also used for the additional modeling described in this document.

The parameters that were varied in the new modeling runs are (1) the size of the paint and coating removal project, (2) the type of project undertaken (furniture, flooring and bathtub) and (3) time lapsed prior to when the paint scrapings were removed from the house. Tables 2-5 of the NMP risk assessment contain a list of other parameters used in the consumer exposure modeling.

The consumer exposure scenarios in the NMP risk assessment were based on the mass of paint and coating removal product that was used by the 50th and 80th percentile consumers from a survey of consumers that reported the use of a paint and coating removal product. This mass of paint and coating removal product was used to determine the amount of painted surface area from which paint could be removed, which was converted into a representative project. In the NMP risk assessment, this was described as, for example a set of shelves, coffee table, bathtub, or a chest of drawers. For this supplemental analysis, consideration was expanded to include the potential for larger consumer projects involving paint and coating removal, such as a dining set (table and chairs) and an entire room floor. An additional model run for the bathtub scenario was included to evaluate exposures if the product was used twice to completely remove paint from the surface of the tub.

Finally, the scenarios modeled in the NMP risk assessment described a consumer that removed the scrapings to an outdoor garbage bin after the second scraping event. A model scenario, or run, was added in this supplemental analysis to evaluate the impact of removing the scrapings more promptly. Removing the scrapings from the room of use could reduce the mass of NMP volatilizing in the room and consequently could reduce exposures for both the user and bystanders.

The minute by minute outputs of these MCCEM runs were entered into a PBPK model developed for the NMP risk assessment.

Tables 1 and 2 summarize the variants in modeling parameters for the additional exposure model runs.

Table 6-1. NMP Consumer Brush- and Roller-Applied Paint Removal Scenario Descriptions and Parameters

Case ID	NMP Released				Removal Method	Room of Use		Rest of House		User Location During Wait and Break Period	Non-User Location
	Wt. Fract.	Area Treated, ft^2	App Rate, sf/min	Release Fraction		Volume, m^3	ACH, hr^{-1}	Volume m^3	ACH, hr^{-1}		
A1	0.5	10 Coffee table	2	0.8695	5-min. brush application, 30-min. wait, and 10-min. scrape per application; process repeated after completion of first scrape. Scrapings removed from house after last scrape.	54	Open windows 1.26	438	0.45	ROH	ROH (entire time)
A2							Closed Windows 0.45				
B1		25 Chest of drawers	2		12.5-min. brush application, 30-min. wait, and 25-min. scrape per application; process repeated after completion of first scrape. Scrapings removed from house after last scrape.		Open windows 1.26				
B2							Closed Windows 0.45				
C1		100 Dining table and 8 chairs	2 (Table) 1 (Chairs)		82-min. brush application, 18-min. wait, and 125-min. scrape per application; process repeated after 30-min. break. Scrapings removed from house after 2nd scrape.		Open windows 1.26				
C2							Closed Windows 0.45				
C3					Same as Scenario C1 except scrapings removed after each scrape.		Open windows 1.26				
D1		240 Floors	4		1-hour roller-application, 1-hour wait, 1.5-hour scrape; process repeated after 1-hour break. Scrapings removed from house after each scrape.		Open windows 1.26				
D2							Closed Windows 0.45				
E1		36 bathtub	2		18-min. brush application, 30-min. wait, and 36-min. scrape per application; process repeated with no break. Scrapings removed from house after 2nd scrape.	Source Cloud 1 m^3 Bathroom 9 m^3	0.18	483	0.18		
E2					Same as Scenario E1 except entire process is repeated after 1-hour break.						

Table 6-2. NMP Consumer Spray-Applied Paint Removal Scenario Descriptions and Parameters

Case ID	NMP Released				Removal Method **	Room of Use		Rest of House		User Location During Wait and Break Period	Non-User Location
	Wt. Fract.	Area Treated, ft^2	App Rate, sf/min	Release Fraction		Volume, m^3	ACH, hr^{-1}	Volume, m^3	ACH, hr^{-1}		
F 1	0.5	100 Dining table and 8 chairs Table (36 sf) Chairs (64 sf)	4 (Table) 2 (Chairs)	0.8695	41-min. spray application, 30-min. wait, and 125-min. scrape per application; process repeated after 1-hour break. Scrapings removed from house after 2nd scrape.	54	Open windows 1.26	438	0.45	ROH	ROH (entire time)
F 2							Closed Windows 0.45				
F 3					Same as Scenario F1 except scrapings removed after each scrape.		Open windows 1.26				
G 1		240 Floors	4 *		1-hour spray application, 1-hour wait, 1.5-hour scrape; process repeated after 1-hour break. Scrapings removed from house after last scrape.		Open windows 1.26				
G 2							Closed Windows 0.45				
H 1		36 bathtub	4		9-min. spray application, 30-min. wait, and 36-min. scrape per application; process repeated with no break. Scrapings removed from house after 2nd scrape.	Source Cloud 1 m^3 Bathroom 9 m^3	0.18	483	0.18		
H 2					Same as Scenario H1 except entire process is repeated after 1-hour break.						

* The application rate for spray-on floors was kept the same as for roll-on floors (Professional Judgment).
** All spray-applied cases use the "high" volatility model, which assumes the first exponential mass increases by 10-fold.
Wt. Fract. = Weight Fraction, ROH=Rest of House

5. Exposure Modeling Results

As in the NMP risk assessment, the indoor air concentrations generated by MCCEM were combined with dermal exposures in a PBPK model. The outputs of that model are the basis for the risk findings for the consumer use of NMP for paint and coating removal in the following scenarios. Calculations are in a reference spreadsheet in a separate appendix titled Appendix B - Spreadsheet: Details of NMP Exposure Model Results.

For the purpose of comparing these higher-end consumer exposures to occupational exposures calculated in the NMP Risk Assessment, EPA also calculated indoor air concentrations using an 8-hour time weighted average (TWA) exposure (see Table D-1 in Appendix D). The PBPK model used the minute-by-minute values generated by MCCEM, not these 8-hour values.

6. Risk Estimation

Risks for acute exposures were estimated for the minute-by-minute exposure concentrations generated by MCCEM and dermal exposures with the PBPK model. The same methodology as was used for the NMP risk assessment with additional risk estimates assuming dermal exposure to NMP during the time of application and scraping. The risks for developmental effects were evaluated with a margin of exposure (MOE) approach using the health hazard value derived in the NMP risk assessment. The hazard value is the peak blood concentration of 216 mg/L and the benchmark MOE (the total of the uncertainty factors) is 30. The evaluation hazard values, their origins, and application to risk estimation are explained in the NMP risk assessment, specifically in sections 3 and 4 (EPA, 2015). The risk estimates for the exposure concentrations in this supplemental analysis are shown in Table 4.

Risks for acute exposures for developmental effects were found for users during larger projects in the additional scenarios evaluated. Risks were only found for non-users in the ROH in the largest project (G2).

Table 6-3 Risk Estimates for Additional Scenarios for Users Assuming Dermal Exposure During Application and Scrapping

Scenario	Glove Use	MOE for POD Cmax 216 mg/L benchmark MOE = 30	
		Cmax (mg/L)	MOE
A1. Coffee Table, Brush Application in Workshop, Windows Open	Gloves	0.27	796
	No Gloves	1.99	108
A2. Coffee Table, Brush Application in Workshop, Windows Closed	Gloves	0.30	718
	No Gloves	2.02	107
	Gloves	0.65	332

Scenario	Glove Use	MOE for POD Cmax 216 mg/L benchmark MOE = 30	
		Cmax (mg/L)	MOE
B1. Chest, Brush Application in Workshop, Windows Open	No Gloves	3.76	58
B2. Chest, Brush Application in Workshop, Windows Closed	Gloves	0.77	282
	No Gloves	3.88	55.7
C1. Dining table and chairs, Brush Application in Workshop, Windows Open	Gloves	3.37	64.1
	No Gloves	13.31	**16.2**
C2. Dining table and chairs, Brush Application in Workshop, Windows Closed	Gloves	4.40	49.0
	No Gloves	14.50	**14.9**
C3. Dining table and chairs, Brush Application in Workshop, Windows Open, Scrapings removed after each scrap	Gloves	2.60	83.2
	No Gloves	12.44	**17.4**
D1. Floors, Roller Application in Workshop, Windows Open	Gloves	4.40	49.1
	No Gloves	11.76	**18.4**
D2. Floors, Roller Application in Workshop, Windows Closed	Gloves	5.58	38.7
	No Gloves	13.36	**16.2**
E1. Bathtub, Brush Application in Bathroom, C_{sat} = 1,013 mg/m^3, 2 Applications	Gloves	4.17	52
	No Gloves	7.81	**28**
E2. Bathtub, Brush Application in Bathroom, C_{sat} = 1,013 mg/m^3, 4 Applications	Gloves	6.39	34
	No Gloves	10.02	**22**
F1. Dining table and chairs, Spray Application in Workshop, Windows Open	Gloves	9.39	**23**
	No Gloves	14.72	**15**
F2. Dining table and chairs, Spray Application in Workshop, Windows Closed	Gloves	12.02	**18.0**
	No Gloves	18.42	**11.7**
F3. Dining table and chairs, Spray Application in Workshop, Windows Open	Gloves	9.27	**23.3**
	No Gloves	14.21	**15.2**
G1. Floors, Spray Application in Workshop, Windows Open	Gloves	23.03	**9.4**
	No Gloves	26.19	**8.2**
G2. Floors, Spray Application in Workshop, Windows Closed	Gloves	30.11	**7.2**
	No Gloves	33.61	**6.4**

Scenario	Glove Use	MOE for POD Cmax 216 mg/L benchmark MOE = 30	
		Cmax (mg/L)	MOE
H1. Bathtub, Spray Application in Bathroom, C_{sat} = 1,013 mg/m^3, 2 Applications	Gloves	22.72	**9.5**
	No Gloves	25.32	**8.5**
H2. Bathtub, Spray Application in Bathroom, C_{sat} = 1,013 mg/m^3, 4 Applications	Gloves	33.64	**6.4**
	No Gloves	38.62	**5.6**

7. Uncertainties and Data Limitations

The modeling of additional scenarios described here has all the same uncertainties listed in the final NMP risk assessment document.

Furthermore, it may be unlikely that a spray-applied paint and coating removal product would be used on projects as large as those modeled in this document. Spray-applied paint and coating removal products may be more useful for surfaces that are curved or irregular and are difficult to cover with a brush or roller. However, this does not prevent the potential use of spray-applied products in the manner modeled.

8. Conclusions

As expected, the larger projects resulted in larger indoor air concentrations of NMP. New 8-hour TWA air concentrations were calculated based on the user's pattern of moving in the home. These updated user behavior adjusted TWA air concentrations are many times larger than those presented in the NMP risk assessment.

The modeling results showed a small decline in exposure when scrapings from the room of use were removed more promptly (i.e. removed after each scrape and within 4 hours rather than at the completion of the project up to 8 hours). However, this variable is not a primary factor in the calculated values from MCCEM.

As expected, the larger projects resulted in higher NMP peak blood concentrations. Risks were identified for developmental effects for the larger projects.

9. References

EPA (US Environmental Protection Agency). 2010. *Multi-Chamber Concentration and Exposure Model (MCCEM) Version 1.2*. https://www.epa.gov/tsca-screening-tools/forms/mccem-multi-chamber-concentration-and-exposure-model-download-and-install (accessed on April 29, 2016).

EPA (U.S. Environmental Protection Agency). 2015. *TSCA Work Plan Chemical Risk Assessment, N-Methylpyrrolidone: Paint Stripper Use, CASRN: 872-50-4.* Office of Pollution

Prevention and Toxics, Washington, DC. https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-work-plan-chemical-risk-assessment-n-0

10. Appendix A

Types of Paint Removal Modeling Scenarios:

A. Coffee table (surface area = 10 ft^2; App. rate = 2 sf/min; Total duration = 90 minutes)
1. Brush-On, Workshop, User in rest of house (ROH) during wait time, ROH=0.45 Air changes per hour (ACH), Workshop = 1.26 ACH, Interzonal air flow (IZ) = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS OPEN)
2. Brush-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 0.45 ACH (= 24.3 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS CLOSED)

B. Chest of drawers (surface area = 25 ft^2; App. rate = 2 sf/min; Total duration = 135 min)
1. Brush-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 1.26 ACH, IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS OPEN)
2. Brush-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 0.45 ACH (= 24.3 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS CLOSED)

C. Dining table and chairs (surface area = 100 ft^2 (36 ft^2 for table and 64 $ft^2$for chairs, 8 @ 8 ft^2); App. rate = 2 sf/min table (18 min), 1 sf/min chairs (64 min); 18 minute wait, Scrape rate 0.8 sf/min (125 min), 30 minute break; Total duration = 8 hours)
1. Brush-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 1.26 ACH, IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS OPEN)
2. Brush-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 0.45 ACH (= 24.3 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS CLOSED)
3. Brush-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 1.26 ACH, IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after each scrape (WINDOWS OPEN)

D. Floor paint removal (surface area = 240 ft^2; App. rate = 4 sf/min; 1 hour wait, Scrape rate = 2.67 (1.5 hour), 1 hour break; Total duration = 8 hours)
1. Roll-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 1.26 ACH, IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after each scrape (WINDOWS OPEN)
2. Roll-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 0.45 ACH (= 24.3 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after each scrape (WINDOWS CLOSED)

E. Bathtub paint removal (surface area = 36 ft^2; App. rate = 2 sf/min; Total duration = 2.8 hours (2 apps); 6.6 hours (4 apps))
1. Brush-On, Bathroom + Source Cloud, User in ROH during wait time, ROH=0.18 ACH, Bathroom = 0.18 ACH, IZ (source cloud/bathroom, bathroom/ROH) = 80 / 35 m^3/hr., 0.5 Weight Fraction (C_{sat} = 1013 mg/m^3), Scrapings removed after 2nd scrape (NO WINDOWS, 2 applications)
2. Brush-On, Bathroom + Source Cloud, User in ROH during wait time, ROH=0.18 ACH, Bathroom =0.18 ACH, IZ (source cloud/bathroom, bathroom/ROH) = 80 / 35 m^3/hr., 0.5 Weight Fraction (C_{sat} = 1013 mg/m^3), Scrapings removed after 2nd and 4th scrapes (NO WINDOWS, 4 applications)

F. Dining table and chairs (surface area = 100 ft^2 (36 ft^2 for table and 64 $ft^2$for chairs, 8 @ 8 ft^2); App. rate = 4 sf/min table (9 min), 2 sf/min chairs (32 min); 30 minute wait, Scrape rate 0.8 sf/min (125 min), 1 hour break; Total duration = 7 hours)

1. Spray-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 1.26 ACH, IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS OPEN)
2. Spray-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 0.45 ACH (= 24.3 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS CLOSED)
3. Spray-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 1.26 ACH, IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after each scrape (WINDOWS OPEN)

G. Floor paint removal (surface area = 240 ft^2; App. rate = 4 sf/min; 1 hour wait, Scrape rate = 2.67 sf/min (1.5 hour), 1 hour break; Total duration = 8 hours)

1. Spray-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 1.26 ACH, IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after each scrape (WINDOWS OPEN)
2. Spray-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 0.45 ACH (= 24.3 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after each scrape (WINDOWS CLOSED)

H. Bathtub paint removal (surface area = 36 ft^2; App. rate = 4 sf/min; Total duration = 2.5 hours (2 apps); 6 hours (4 apps))

1. Spray-On, Bathroom + Source Cloud, User in ROH during wait time, ROH=0.18 ACH, Bathroom = 0.18 ACH, IZ (source cloud/bathroom, bathroom/ROH) = 80 / 35 m^3/hr., 0.5 Weight Fraction (Csat = 1013 mg/m^3), Scrapings removed after 2nd scrape (NO WINDOWS, 2 applications)
2. Spray -On, Bathroom + Source Cloud, User in ROH during wait time, ROH=0.18 ACH, Bathroom =0.18 ACH, IZ (source cloud/bathroom, bathroom/ROH) = 80 / 35 m^3/hr., 0.5 Weight Fraction (Csat = 1013 mg/m^3), Scrapings removed after 2nd and 4th scrapes (NO WINDOWS, 4 applications)

Unchanged modeling parameters for all scenarios

- House volume = 492 m^3
- Paint stripper consumer weight fraction = 0.5 (upper end)
- Non-user location = ROH (entire time)

Table A-1. Time Schedule for Brush- and Roller-Applied Paint and Coating Removal with Repeat Application

Scenario	Elapsed Time From Time Zero, Minutes (Product User Location)						
	Apply 1	***Wait 1***	***Scrape 1***	***Break***	***Apply 2***	***Wait 2***	***Scrape 2***
A. Brush application to coffee table in workshop, central tendency scenario *(App rate = 2 sf/min)*	0-5 (Workshop)	5-35 (ROH)	35-45 (Workshop)	0	45-50 (Workshop)	50-80 (ROH)	80-90 (Workshop)
B. Brush application to chest in workshop, upper-end scenario for user & non-user *(App rate = 2 sf/min)*	0-12.5 (Workshop)	12.5-42.5 (ROH)	42.5-67.5 (Workshop)	0	67.5-80 (Workshop)	80-110 (ROH)	110-135 (Workshop)
C. Brush application to dining table and chairs in workshop, central tendency scenario *(App rate = 2 sf/min for table; 1 sf/min for chairs)*	0-82 (Workshop)	82-100 (ROH)	100-225 (Workshop)	225-255 (ROH)	255-337 (Workshop)	337-355 (ROH)	355-480 (Workshop)
D. Roller application to floor *(App rate = 4 sf/min)*	0-60 (Workshop)	60-120 (ROH)	120-210 (Workshop)	210-270 (ROH)	270-330 (Workshop)	330-390 (ROH)	390-480 (Workshop)
E. Brush application to bathtub *(App rate = 2 sf/min)*							
E1 = 2 applications	0-18 (Src Cloud)	18-48 (ROH)	48-84 (Src Cloud)	0	84-102 (Src Cloud)	102-132 (ROH)	132-168 (Src Cloud)
E2 = 4 apps (repeat 1st 2 apps after 1 hour break, total time = 396 min.)	228-246 (Src Cloud)	246-276 (ROH)	276-312 (Src Cloud)		312-330 (Src Cloud)	330-360 (ROH)	360-396 (Src Cloud)

155

Table A-2. Time Schedule for Spray-Applied Paint and Coating Removal with Repeat Application

Scenario	Elapsed Time From Time Zero, Minutes (Product User Location)						
	Apply 1	***Wait 1***	***Scrape 1***	***Break***	***Apply 2***	***Wait 2***	***Scrape 2***
F. Spray application to dining table and chairs in workshop, central tendency scenario *(App rate = 4 sf/min for table; 2 sf/min for chairs)*	0-41 (Workshop)	41-71 (ROH)	71-196 (Workshop)	196-256 (ROH)	256-297 (Workshop)	297-327 (ROH)	327-452 (Workshop)
G. Spray application to floors *(App rate = 4 sf/min)*	0-60 (Workshop)	60-120 (ROH)	120-210 (Workshop)	210-270 (ROH)	270-330 (Workshop)	330-390 (ROH)	390-480 (Workshop)
H. Spray application to bathtub *(App rate = 4 sf/min)*							
H1 = 2 applications	0-9 (Src Cloud)	9-39 (ROH)	39-75 (Src Cloud)	0	75-84 (Src Cloud)	84-114 (ROH)	114-150 (Src Cloud)
H2 = 4 apps (repeat 1st 2 apps after 1 hour break, total time = 360 min.)	210-219 (Src Cloud)	219-249 (ROH)	249-285 (Src Cloud)		285-294 (Src Cloud)	294-324 (ROH)	324-360 (Src Cloud)

156 Src Cloud = Source Cloud

157 D.5 MCCEM Inhalation Modeling Case Summaries

158

159

160

161

162 ***NMP Summaries***

163 Formula: C5H9NO

164 CASRN: 872-50-4

Molecular Weight:	99.13 g/mol
Density:	1.028 g/cm^2 (liquid)
Appearance:	clear liquid
Melting Point:	-24 °C = -11 °F = 249 K
Boiling Point:	203 °C = 397 °F = 476 K
Conversion units: 1 ppm =	4.054397 mg/m^3
Saturation Concentration:	~1,013 mg/m^3 (equivalent to a vapor pressure of 0.190 Torr at 25 °C, used in Scenario 5, based on (OECD, 2007a). See Section D.3)
Saturation Concentration:	~640 mg/m^3 (representing the upper end of the saturation concentration values associated with "normal humidity conditions." See Section D.3)

NMP Scenario A1. Coffee Table, Brush-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 1.26 ACH (= 68 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS OPEN)

MCCEM Input Summary

Application Method:

Brush-on`

Volumes:

Workshop volume = 54 m^3

ROH volume = 492 – 54 = 438 m^3

Airflows:

Workshop-outdoors	68 m^3/h
ROH-outdoors	197.1 m^3/h (0.45 ACH)
Workshop-ROH	107 m^3/h

NMP Mass Released:

Coffee table = 10 sq. ft. surface area

Applied product mass = 108 g/sq. ft. = 1,080 g

Applied NMP = 1,080 g × 0.5 (wt. fraction) = 540 g

Total NMP mass released (theoretical, both exponentials) = 1,080 g × 0.5 (wt. fraction) × 0.8695 (release fraction, theoretical) = 469.53 g

Mass released per app = 234.77 g

For each of the 2 applications:

k_1 = 32.83/hr.

% Mass for Exponential 1 = 0.7% of Total mass applied = 0.007/0.8695 = 0.8% of released NMP

E_{01} = Mass * k_1 = 0.008*234.77*32.83 = 61.7 g/hr. (**NOTE:** only k and Mass are needed as inputs)

k_2 = 0.00237/hr.

% Mass for Exponential 2 = 86.2% of applied NMP = 0.862/0.8695 = 99.2% of released NMP

E_{02} = Mass * k_2 = 0.992*234.77*0.00237 = 0.55 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

Episode	Elapsed Time from Time Zero, Minutes (Product User Location)					
	Apply 1	***Wait 1***	***Scrape 1***	***Apply 2***	***Wait 2***	***Scrape 2***
A1) Coffee Table, Brush-On, Workshop, User ROH during wait time, 0.45 ACH, 0.5 Weight Fraction, WINDOWS OPEN	0-5 (Wkshp)	5-35 (ROH)	35-45 (Wkshp)	45-50 (Wkshp)	50-80 (ROH)	80-90 (Wkshp)

User in ROH at the end of Scraping 2

User in ROH for the remainder of the run (22 hours, 30 minutes)

Model Run Time:
0-24 hours
User takes out scrapings after 90 minutes; emissions truncated.

NMP Scenario A2. Coffee Table, Brush-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 0.45 ACH (= 24.3 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS CLOSED)

MCCEM Input Summary

Application Method:

Brush-on

Volumes:

Workshop volume = 54 m^3

ROH volume = 492 – 54 = 438 m^3

Airflows:

Workshop-outdoors	24.3 m^3/h
ROH-outdoors	197.1 m^3/h (0.45 ACH)
Workshop-ROH	107 m^3/h

NMP Mass Released:

Coffee table = 10 sq. ft. surface area

Applied product mass = 108 g/sq. ft. = 1,080 g

Applied NMP = 1,080 g × 0.5 (wt. fraction) = 540 g

Total NMP mass released (theoretical, both exponentials) = 1,080 g × 0.5 (wt. fraction) × 0.8695 (release fraction, theoretical) = 469.53 g

Mass released per app = 234.77 g

For each of the 2 applications:

k_1 = 32.83/hr.

% Mass for Exponential 1 = 0.7% of Total mass applied = 0.007/0.8695 = 0.8% of released NMP

E_{01} = Mass * k_1 = 0.008*234.77*32.83 = 61.7 g/hr. (**NOTE:** only k and Mass are needed as inputs)

k_2 = 0.00237/hr.

% Mass for Exponential 2 = 86.2% of applied NMP = 0.862/0.8695 = 99.2% of released NMP

E_{02} = Mass * k_2 = 0.862*234.77*0.00237 = 0.55 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

Episode	Elapsed Time from Time Zero, Minutes (Product User Location)					
	Apply 1	***Wait 1***	***Scrape 1***	***Apply 2***	***Wait 2***	***Scrape 2***
A2) Coffee Table, Brush-On, Workshop, User ROH during wait time, 0.45 ACH, 0.5 Weight Fraction, WINDOWS CLOSED	0-5 (Wkshp)	5-35 (ROH)	35-45 (Wkshp)	45-50 (Wkshp)	50-80 (ROH)	80-90 (Wkshp)

User in ROH at the end of Scraping 2

User in ROH for the remainder of the run (22 hours, 30 minutes)

Model Run Time:
0-24 hours
User takes out scrapings after 90 minutes; emissions truncated.

NMP Scenario B1. Chest, Brush-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 1.26 ACH (= 68 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS OPEN)

MCCEM Input Summary

Application Method:

Brush-on

Volumes:

Workshop volume = 54 m^3

ROH volume = 492 – 54 = 438 m^3

Airflows:

Workshop-outdoors	68 m^3/h
ROH-outdoors	197.1 m^3/h (0.45 ACH)
Workshop-ROH	107 m^3/h

NMP Mass Released:

Chest = 25 sq. ft. surface area

Applied product mass = 2,700 g

Applied NMP = 2,700 g × 0.5 (wt. fraction) = 1,350 g

Total NMP mass released (both exponentials) = 2,700 g × 0.5 (wt. fraction) × 0.8695 (release fraction, theoretical) =1173.8 g

Mass released per app = 586.9 g

For each of the 2 applications:

k_1 = 32.83/hr

% Mass for Exponential 1 = 0.7% of Total mass applied = 0.007/0.8695 = 0.8% of released NMP

E_{01} = Mass * k_1 = 0.008*586.9*32.83 = 154.1 g/hr. (**NOTE:** only k and Mass are needed as inputs)

k_2 = 0.00237/hr

% Mass for Exponential 2 = 86.2% of applied NMP = 0.862/0.8695 = 99.2% of released NMP

E_{02} = Mass * k_2 = 0.992*586.9*0.00237 = 1.38 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

Episode	**Elapsed Time from Time Zero, Minutes (Product User Location)**					
	Apply 1	***Wait 1***	***Scrape 1***	***Apply 2***	***Wait 2***	***Scrape 2***
B1) Chest, Brush-On, Workshop, User in ROH during wait time, 0.45 ACH, 0.5 Weight Fraction, WINDOWS OPEN	0-12.5 (Wkshp)	12.5-42.5 (ROH)	42.5-67.5 (Wkshp)	67.5-80 (Wkshp)	80-110 (ROH)	110-135 (Wkshp)

User in ROH at the end of Scraping 2

User in ROH for the remainder of the run (21 hours, 45 minutes)

Model Run Time:
0-24 hours
User takes out scrapings after 135 minutes; emissions truncated.

NMP Scenario B2. Chest, Brush-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 0.45 ACH (= 24.3 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS CLOSED)

MCCEM Input Summary

Application Method:

Brush-on

Volumes:

Workshop volume = 54 m^3

ROH volume = 492 – 54 = 438 m^3

Airflows:

Workshop-outdoors	24.3 m^3/h
ROH-outdoors	197.1 m^3/h (0.45 ACH)
Workshop-ROH	107 m^3/h

NMP Mass Released:

Chest = 25 sq. ft. surface area

Applied product mass = 2,700 g

Applied NMP = 2,700 g × 0.5 (wt. fraction) = 1,350 g

Total NMP mass released (both exponentials) = 2,700 g × 0.5 (wt. fraction) × 0.8695 (release fraction, theoretical) =1173.8 g

Mass released per app = 586.9 g

For each of the 2 applications:

k_1 = 32.83/hr.

% Mass for Exponential 1 = 0.7% of Total mass applied = 0.007/0.8695 = 0.8% of released NMP

E_{01} = Mass * k_1 = 0.008*586.9*32.83 = 154.1 g/hr. (**NOTE:** only k and Mass are needed as inputs)

k_2 = 0.00237/hr.

% Mass for Exponential 2 = 86.2% of applied NMP = 0.862/0.8695 = 99.2% of released NMP

E_{02} = Mass * k_2 = 0.992*586.9*0.00237 = 1.38 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

Episode	**Elapsed Time from Time Zero, Minutes (Product User Location)**					
	Apply 1	***Wait 1***	***Scrape 1***	***Apply 2***	***Wait 2***	***Scrape 2***
B2) Chest, Brush-On, Workshop, User in ROH during wait time, 0.45 ACH, 0.5 Weight Fraction, WINDOWS CLOSED	0-12.5 (Wkshp)	12.5-42.5 (ROH)	42.5-67.5 (Wkshp)	67.5-80 (Wkshp)	80-110 (ROH)	110-135 (Wkshp)

User in ROH at the end of Scraping 2

User in ROH for the remainder of the run (21 hours, 45 minutes)

Model Run Time:
0-24 hours
User takes out scrapings after 135 minutes; emissions truncated.

NMP Scenario C1. Dining table and chairs, Brush-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 1.26 ACH (= 68 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS OPEN)

MCCEM Input Summary

Application Method: Brush-on

Volumes: Workshop volume = 54 m^3
ROH volume = 492 – 54 = 438 m^3

Airflows:

Workshop-outdoors	68 m^3/h
ROH-outdoors	197.1 m^3/h (0.45 ACH)
Workshop-ROH	107 m^3/h

NMP Mass Released:

Table = 36 sq. ft. surface area; Chairs = 64 sq. ft. surface area
Applied product mass = 10,800 g
Applied NMP = 10,800 g × 0.5 (wt. fraction) = 5,400 g
Total NMP mass released (both exponentials) = 10,800 g × 0.5 (wt. fraction) × 0.8695 (release fraction, theoretical) =4695.3 g
Mass released per app = 2347.65 g

For each of the 2 applications:

k_1 = 32.83/hr.

% Mass for Exponential 1 = 0.7% of Total mass applied = 0.007/0.8695 = 0.8% of released NMP

E_{01} = Mass * k_1 = 0.008*2347.65*32.83 = 616.6 g/hr. (**NOTE:** only k and Mass are needed as inputs)

k_2 = 0.00237/hr.

% Mass for Exponential 2 = 86.2% of applied NMP = 0.862/0.8695 = 99.2% of released NMP

E_{02} = Mass * k_2 = 0.992*2347.65*0.00237 = 5.52 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

	Elapsed Time from Time Zero, Minutes (Product User Location)						
Episode	***Apply 1***	***Wait 1***	***Scrape 1***	***Break***	***Apply 2***	***Wait 2***	***Scrape 2***
C1) Dining table and chairs, Brush-On, Workshop, User in ROH during wait time, 0.45 ACH, 0.5 Weight Fraction, WINDOWS OPEN	0-82 (Wkshp)	82-100 (ROH)	100-225 (Wkshp)	225-255 (ROH)	255-337 (Wkshp)	337-355 (ROH)	355-480 (Wkshp)

User in ROH at the end of Scraping 2
User in ROH for the remainder of the run (16 hours)

Model Run Time:
0-24 hours
User takes out scrapings after 480 minutes; emissions truncated.

NMP Scenario C2. Dining table and chairs, Brush-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 0.45 ACH (= 24.3 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS CLOSED)

MCCEM Input Summary

Application Method:

Brush-on

Volumes:

Workshop volume = 54 m^3

ROH volume = 492 – 54 = 438 m^3

Airflows:

Workshop-outdoors	24.3 m^3/h
ROH-outdoors	197.1 m^3/h (0.45 ACH)
Workshop-ROH	107 m^3/h

NMP Mass Released:

Table = 36 sq. ft. surface area; Chairs = 64 sq. ft. surface area

Applied product mass = 10,800 g (Application rate = 108 g/sf)

Applied NMP = 10,800 g × 0.5 (wt. fraction) = 5,400 g

Total NMP mass released (both exponentials) = 10,800 g × 0.5 (wt. fraction) × 0.8695 (release fraction, theoretical) =4695.3 g

Mass released per app = 2347.65 g

For each of the 2 applications:

k_1 = 32.83/hr.

% Mass for Exponential 1 = 0.7% of Total mass applied = 0.007/0.8695 = 0.8% of released NMP

E_{01} = Mass * k_1 = 0.008*2347.65*32.83 = 616.6 g/hr. (**NOTE:** only k and Mass are needed as inputs)

k_2 = 0.00237/hr.

% Mass for Exponential 2 = 86.2% of applied NMP = 0.862/0.8695 = 99.2% of released NMP

E_{02} = Mass * k_2 = 0.992*2347.65*0.00237 = 5.52 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

	Elapsed Time from Time Zero, Minutes (Product User Location)						
Episode	***Apply 1***	***Wait 1***	***Scrape 1***	***Break***	***Apply 2***	***Wait 2***	***Scrape 2***
C2) Dining table and chairs, Brush-On, Workshop, User in ROH during wait time, 0.45 ACH, 0.5 Weight Fraction, WINDOWS CLOSED	0-82 (Wkshp)	82-100 (ROH)	100-225 (Wkshp)	225-255 (ROH)	255-337 (Wkshp)	337-355 (ROH)	355-480 (Wkshp)

User in ROH at the end of Scraping 2

User in ROH for the remainder of the run (16 hours)

Model Run Time:

0-24 hours

User takes out scrapings after 480 minutes; emissions truncated.

NMP Scenario C3. Dining table and chairs, Brush-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 1.26 ACH (= 68 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after each scrape (WINDOWS OPEN)

MCCEM Input Summary

Application Method:

Brush-on

Volumes:

Workshop volume = 54 m^3

ROH volume = 492 – 54 = 438 m^3

Airflows:

Workshop-outdoors	68 m^3/h
ROH-outdoors	197.1 m^3/h (0.45 ACH)
Workshop-ROH	107 m^3/h

NMP Mass Released:

Table = 36 sq. ft. surface area; Chairs = 64 sq. ft. surface area

Applied product mass = 10,800 g (Application rate = 108 g/sf)

Applied NMP = 10,800 g × 0.5 (wt. fraction) = 5,400 g

Total NMP mass released (both exponentials) = 10,800 g × 0.5 (wt. fraction) × 0.8695 (release fraction, theoretical) =4695.3 g

Mass released per app = 2347.65 g

For each of the 2 applications:

k_1 = 32.83/hr.

% Mass for Exponential 1 = 0.7% of Total mass applied = 0.007/0.8695 = 0.8% of released NMP

E_{01} = Mass * k_1 = 0.008*2347.65*32.83 = 616.6 g/hr. (**NOTE:** only k and Mass are needed as inputs)

k_2 = 0.00237/hr.

% Mass for Exponential 2 = 86.2% of applied NMP = 0.862/0.8695 = 99.2% of released NMP

E_{02} = Mass * k_2 = 0.992*2347.65*0.00237 = 5.52 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

	Elapsed Time from Time Zero, Minutes (Product User Location)						
Episode	***Apply 1***	***Wait 1***	***Scrape 1***	***Break***	***Apply 2***	***Wait 2***	***Scrape 2***
C3) Dining table and chairs, Brush-On, Workshop, User in ROH during wait time, 0.45 ACH, 0.5 Weight Fraction, WINDOWS OPEN	0-82 (Wkshp)	82-100 (ROH)	100-225 (Wkshp)	225-255 (ROH)	255-337 (Wkshp)	337-355 (ROH)	355-480 (Wkshp)

User in ROH at the end of Scraping 2

User in ROH for the remainder of the run (16 hours)

Model Run Time:

0-24 hours

User takes out scrapings after 225 and 480 minutes; emissions truncated.

NMP Scenario D1. Floor, Brush-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 1.26 ACH (= 68 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after each scrape (WINDOWS OPEN)

MCCEM Input Summary

Application Method:

Brush-on

Volumes:

Workshop volume = 54 m^3

ROH volume = 492 – 54 = 438 m^3

Airflows:

Workshop-outdoors	68 m^3/h
ROH-outdoors	197.1 m^3/h (0.45 ACH)
Workshop-ROH	107 m^3/h

NMP Mass Released:

Floor = 240 sq. ft. surface area

Applied product mass = 25,920 g (Application rate = 108 g/sf)

Applied NMP = 25,920 g × 0.5 (wt. fraction) = 12,960 g

Total NMP mass released (both exponentials) = 25,920 g × 0.5 (wt. fraction) × 0.8695 (release fraction, theoretical) =11,268.7 g

Mass released per app = 5634.4 g

For each of the 2 applications:

k_1 = 32.83/hr.

% Mass for Exponential 1 = 0.7% of Total mass applied = 0.007/0.8695 = 0.8% of released NMP

E_{01} = Mass * k_1 = 0.008*5634.4*32.83 = 1479.8 g/hr. (**NOTE:** only k and Mass are needed as inputs)

k_2 = 0.00237/hr.

% Mass for Exponential 2 = 86.2% of applied NMP = 0.862/0.8695 = 99.2% of released NMP

E_{02} = Mass * k_2 = 0.992*5634.4*0.00237 = 13.25 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

	Elapsed Time from Time Zero, Minutes (Product User Location)						
Episode	***Apply 1***	***Wait 1***	***Scrape 1***	***Break***	***Apply 2***	***Wait 2***	***Scrape 2***
D1) Floor, Roll-on, Workshop, User in ROH during wait time, 0.45 ACH, 0.5 Weight Fraction, WINDOWS OPEN	0-60 (Wkshp)	60-120 (ROH)	120-210 (Wkshp)	210-270 (ROH)	270-330 (Wkshp)	330-390 (ROH)	390-480 (Wkshp)

User in ROH at the end of Scraping 2

User in ROH for the remainder of the run (16 hours)

Model Run Time:
0-24 hours
User takes out scrapings after 210 and 480 minutes; emissions truncated.

NMP Scenario D2. Floor, Brush-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 0.45 ACH (= 24.3 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after each scrape (WINDOWS CLOSED)

MCCEM Input Summary

Application Method:

Brush-on

Volumes:

Workshop volume = 54 m^3

ROH volume = 492 – 54 = 438 m^3

Airflows:

Workshop-outdoors	24.3 m^3/h
ROH-outdoors	197.1 m^3/h (0.45 ACH)
Workshop-ROH	107 m^3/h

NMP Mass Released:

Floor = 240 sq. ft. surface area

Applied product mass = 25,920 g (Application rate = 108 g/sf)

Applied NMP = 25,920 g × 0.5 (wt. fraction) = 12,960 g

Total NMP mass released (both exponentials) = 25,920 g × 0.5 (wt. fraction) × 0.8695 (release fraction, theoretical) =11,268.7 g

Mass released per app = 5634.4 g

For each of the 2 applications:

k_1 = 32.83/hr.

% Mass for Exponential 1 = 0.7% of Total mass applied = 0.007/0.8695 = 0.8% of released NMP

E_{01} = Mass * k_1 = 0.008*5634.4*32.83 = 1479.8 g/hr. (**NOTE:** only k and Mass are needed as inputs)

k_2 = 0.00237/hr.

% Mass for Exponential 2 = 86.2% of applied NMP = 0.862/0.8695 = 99.2% of released NMP

E_{02} = Mass * k_2 = 0.992*5634.4*0.00237 = 13.25 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

	Elapsed Time from Time Zero, Minutes (Product User Location)						
Episode	***Apply 1***	***Wait 1***	***Scrape 1***	***Break***	***Apply 2***	***Wait 2***	***Scrape 2***
D2) Floor, Roll-on, Workshop, User in ROH during wait time, 0.45 ACH, 0.5 Weight Fraction, WINDOWS CLOSED	0-60 (Wkshp)	60-120 (ROH)	120-210 (Wkshp)	210-270 (ROH)	270-330 (Wkshp)	330-390 (ROH)	390-480 (Wkshp)

User in ROH at the end of Scraping 2

User in ROH for the remainder of the run (16 hours)

Model Run Time:
0-24 hours
User takes out scrapings after 210 and 480 minutes; emissions truncated

NMP Scenario E1. Bathroom, Brush-On, Bathroom + Source Cloud, User in ROH during wait time, ROH=0.18 ACH, Bathroom = 0.18 ACH, IZ (source cloud/bathroom, bathroom/ROH) = 80, 35 m^3/hr., 0.5 Weight Fraction (Csat = 1013 mg/m^3), Scrapings removed after 2nd scrape (WINDOWS CLOSED, 2 applications)

MCCEM Input Summary

MCCEM saturation concentration constraint invoked at 1013 mg/m^3

Application Method: Brush-on

Volumes:

Bathroom Volume = 9 m^3 (8 m^3 after subtracting source cloud zone)

Source Cloud Volume = 1 m^3

ROH volume = 492 – 9 = 483 m^3

Airflows:

Bathroom-outdoors	1.6 m^3/h
Source cloud - bathroom	80 m^3/h
Source cloud - outdoors	0
ROH-outdoors	86.9 m^3/h (0.18 ACH)
Bathroom-ROH	35 m^3/h

NMP Mass Released:

Bathtub = 36 sq. ft. surface area

Applied product mass = 3,888 g (Application rate = 108 g/sf)

Applied NMP = 3,888 g × 0.5 (wt. fraction) = 1,944 g

Total NMP mass released (both exponentials) = 3,888 g × 0.5 (wt. fraction) × 0.8695 (release fraction, theoretical) = 1690.3 g

Mass released per app = 845.15 g

For each of the 2 applications:

$\mathbf{k_1}$ = 32.83/hr.

% Mass for Exponential 1 = 0.7% of Total mass applied = 0.007/0.8695 = 0.8% of released NMP

$\mathbf{E_{01}}$ = Mass * k_1 = 0.008*845.15.4*32.83 = 222.0 g/hr. (**NOTE:** only k and Mass are needed as inputs)

$\mathbf{k_2}$ = 0.00237/hr.

% Mass for Exponential 2 = 86.2% of applied NMP = 0.862/0.8695 = 99.2% of released NMP

$\mathbf{E_{02}}$ = Mass * k_2 = 0.992*845.15*0.00237 = 1.99 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

Episode	Elapsed Time from Time Zero, Minutes (Product User Location)					
	Apply 1	***Wait 1***	***Scrape 1***	***Apply 2***	***Wait 2***	***Scrape 2***
E1) Bathtub, Brush-On, Bathroom + Source Cloud, User in ROH during wait time, 0.18 ACH, 0.5 Wt. Fract.	0-18 (SrcCloud)	18-48 (ROH)	48-84 (SrcCloud)	84-102 (SrcCloud)	102-132 (ROH)	132-168 (SrcCloud)

User in ROH at the end of Scraping 2
User in ROH for the remainder of the run (21 hours, 12 minutes)

Model Run Time:
0-24 hours
User takes out scrapings after 168 minutes; emissions truncated.

NMP Scenario E2. Bathroom, Brush-On, Bathroom + Source Cloud, User in ROH during wait time, ROH=0.18 ACH, Bathroom = 0.18 ACH, IZ (source cloud/bathroom, bathroom/ROH) = 80, 35 m^3/hr., 0.5 Weight Fraction (Csat = 1013 mg/m^3), Scrapings removed after 2nd and 4th scrapes (WINDOWS CLOSED, 4 applications)

MCCEM Input Summary

MCCEM saturation concentration constraint invoked at 1013 mg/m^3

Application Method: Brush-on

Volumes:

Bathroom Volume = 9 m^3 (8 m^3 after subtracting source cloud zone)

Source Cloud Volume = 1 m^3

ROH volume = 492 – 9 = 483 m^3

Airflows:

Bathroom-outdoors	1.6 m^3/h
Source cloud - bathroom	80 m^3/h
Source cloud - outdoors	0
ROH-outdoors	86.9 m^3/h (0.18 ACH)
Bathroom-ROH	35 m^3/h

NMP Mass Released:

Bathtub = 36 sq. ft. surface area

Applied product mass = 3,888 g (Application rate = 108 g/sf)

Applied NMP = 3,888 g × 0.5 (wt. fraction) = 1,944 g

Total NMP mass released (both exponentials) = 3,888 g × 0.5 (wt. fraction) × 0.8695 (release fraction, theoretical) = 1690.3 g

Mass released per app = 845.15 g

For each of the 2 applications:

k_1 = 32.83/hr.

% Mass for Exponential 1 = 0.7% of Total mass applied = 0.007/0.8695 = 0.8% of released NMP

E_{01} = Mass * k_1 = 0.008*845.15.4*32.83 = 222.0 g/hr. (**NOTE:** only k and Mass are needed as inputs)

k_2 = 0.00237/hr.

% Mass for Exponential 2 = 86.2% of applied NMP = 0.862/0.8695 = 99.2% of released NMP

E_{02} = Mass * k_2 = 0.992*845.15*0.00237 = 1.99 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

Episode	Elapsed Time from Time Zero, Minutes (Product User Location)					
	Apply 1 & 3	***Wait 1 & 3***	***Scrape 1 & 3***	***Apply 2 &4***	***Wait 2 &4***	***Scrape 2 &4***
	E2) Bathtub, Brush-On, Bathroom + Source Cloud, User in ROH during wait time, 0.18 ACH, 0.5 Weight Fraction					
1st and 2nd Application	0-18 (SrcCloud)	18-48 (ROH)	48-84 (SrcCloud)	84-102 (SrcCloud)	102-132 (ROH)	132-168 (SrcCloud)
3rd and 4th Application	228-246 (SrcCloud)	246-276 (ROH)	276-312 (SrcCloud)	312-330 (SrcCloud)	330-360 (ROH)	360-396 (SrcCloud)

User in ROH at the end of Scraping 2 and 4
User in ROH for the remainder of the run (17 hours, 24 minutes)

Model Run Time:
0-24 hours
User takes out scrapings after 168 and 396 minutes; emissions truncated.

NMP Scenario F1. Dining table and chairs, Spray-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 1.26 ACH (= 68 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS OPEN)

MCCEM Input Summary

Application Method: Spray-on

Volumes: Workshop volume = 54 m^3

ROH volume = 492 – 54 = 438 m^3

Airflows:

Workshop-outdoors	68 m^3/h
ROH-outdoors	197.1 m^3/h (0.45 ACH)
Workshop-ROH	107 m^3/h

NMP Mass Released:

Table = 36 sq. ft. surface area; Chairs = 64 sq. ft. surface area

Applied product mass = 8,100 g (Application rate = 81 g/sf)

Overspray = 0.05*8,100 g = 405 g

Total Product Mass = 8,100 + 405 = 8,505 g

Total NMP Mass = 8,505 g × 0.5 (wt. fraction) = 4,252.5 g

Total NMP mass released (both exponentials) = 4,252.5 x 0.8695 (release fraction, theoretical) = 3697.5 g

Mass released per app = 1848.8 g

For each of the 2 applications:

k_1 = 32.83/hr.

% Mass for Exponential 1 = 7.0% of Total mass applied = 0.07/0.8695 = 8% of released NMP

E_{01} = Mass * k_1 = 0.08*1848.8*32.83 = 4855.7 g/hr. (**NOTE:** only k and Mass are needed as inputs)

k_2 = 0.00237/hr.

% Mass for Exponential 2 = 79.95% of applied NMP = 0.7995/0.8695 = 91.9% of released NMP

E_{02} = Mass * k_2 = 0.919*1848.8*0.00237 = 4.03 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

	Elapsed Time from Time Zero, Minutes (Product User Location)						
Episode	***Apply 1***	***Wait 1***	***Scrape 1***	***Break***	***Apply 2***	***Wait 2***	***Scrape 2***
F1) Dining table and chairs, Spray-On, Workshop, User in ROH during wait time, 0.45 ACH, 0.5 Weight Fraction, WINDOWS OPEN	0-41 (Wkshp)	41-71 (ROH)	71-196 (Wkshp)	196-256 (ROH)	256-297 (Wkshp)	297-327 ROH)	327-452 (Wkshp)

User in ROH at the end of Scraping 2

User in ROH for the remainder of the run (16 hours, 28 minutes)

Model Run Time:
0-24 hours
User takes out scrapings after 452 minutes; emissions truncated.

NMP Scenario F2. Dining table and chairs, Spray-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 0.45 ACH (= 24.3 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after 2nd scrape (WINDOWS CLOSED)

MCCEM Input Summary

Application Method: Spray-on

Volumes: Workshop volume = 54 m^3

ROH volume = 492 – 54 = 438 m^3

Airflows:

Workshop-outdoors	24.3 m^3/h
ROH-outdoors	197.1 m^3/h (0.45 ACH)
Workshop-ROH	107 m^3/h

NMP Mass Released:

Table = 36 sq. ft. surface area; Chairs = 64 sq. ft. surface area

Applied product mass = 8,100 g (Application rate = 81 g/sf)

Overspray = 0.05*8,100 g = 405 g

Total Product Mass = 8,100 + 405 = 8,505 g

Total NMP Mass = 8,505 g × 0.5 (wt. fraction) = 4,252.5 g

Total NMP mass released (both exponentials) = 4,252.5 x 0.8695 (release fraction, theoretical) = 3697.5 g

Mass released per app = 1848.8 g

For each of the 2 applications:

$\mathbf{k_1}$ = 32.83/hr.

% Mass for Exponential 1 = 7.0% of Total mass applied = 0.07/0.8695 = 8% of released NMP

$\mathbf{E_{01}}$ = Mass * k_1 = 0.08*1848.8*32.83 = 4855.7 g/hr. (**NOTE:** only k and Mass are needed as inputs)

$\mathbf{k_2}$ = 0.00237/hr.

% Mass for Exponential 2 = 79.95% of applied NMP = 0.7995/0.8695 = 91.9% of released NMP

$\mathbf{E_{02}}$ = Mass * k_2 = 0.919*1848.8*0.00237 = 4.03 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

Episode	Elapsed Time from Time Zero, Minutes (Product User Location)						
	Apply 1	***Wait 1***	***Scrape 1***	***Break***	***Apply 2***	***Wait 2***	***Scrape 2***
F2) Dining table and chairs, Spray-On, Workshop, User in ROH during wait time, 0.45 ACH, 0.5 Weight Fraction, WINDOWS CLOSED	0-41 (Wkshp)	41-71 (ROH)	71-196 (Wkshp)	196-256 (ROH)	256-297 (Wkshp)	297-327 ROH)	327-452 (Wkshp)

User in ROH at the end of Scraping 2

User in ROH for the remainder of the run (16 hours, 28 minutes)

Model Run Time:
0-24 hours
User takes out scrapings after 452 minutes; emissions truncated.

NMP Scenario F3. Dining table and chairs, Spray-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 1.26 ACH (= 68 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after each scrape (WINDOWS OPEN)

MCCEM Input Summary

Application Method: Spray-on

Volumes: Workshop volume = 54 m^3

ROH volume = 492 – 54 = 438 m^3

Airflows:

Workshop-outdoors	68 m^3/h
ROH-outdoors	197.1 m^3/h (0.45 ACH)
Workshop-ROH	107 m^3/h

NMP Mass Released:

Table = 36 sq. ft. surface area; Chairs = 64 sq. ft. surface area

Applied product mass = 8,100 g (Application rate = 81 g/sf)

Overspray = 0.05*8,100 g = 405 g

Total Product Mass = 8,100 + 405 = 8,505 g

Total NMP Mass = 8,505 g × 0.5 (wt. fraction) = 4,252.5 g

Total NMP mass released (both exponentials) = 4,252.5 x 0.8695 (release fraction, theoretical) = 3697.5 g

Mass released per app = 1848.8 g

For each of the 2 applications:

$\mathbf{k_1}$ = 32.83/hr.

% Mass for Exponential 1 = 7.0% of Total mass applied = 0.07/0.8695 = 8% of released NMP

$\mathbf{E_{01}}$ = Mass * k_1 = 0.08*1848.8*32.83 = 4855.7 g/hr. (**NOTE:** only k and Mass are needed as inputs)

$\mathbf{k_2}$ = 0.00237/hr.

% Mass for Exponential 2 = 79.95% of applied NMP = 0.7995/0.8695 = 91.9% of released NMP

$\mathbf{E_{02}}$ = Mass * k_2 = 0.919*1848.8*0.00237 = 4.03 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

	Elapsed Time from Time Zero, Minutes (Product User Location)						
Episode	***Apply 1***	***Wait 1***	***Scrape 1***	***Break***	***Apply 2***	***Wait 2***	***Scrape 2***
F3) Dining table and chairs, Spray-On, Workshop, User in ROH during wait time, 0.45 ACH, 0.5 Weight Fraction, WINDOWS OPEN	0-41 (Wkshp)	41-71 (ROH)	71-196 (Wkshp)	196-256 (ROH)	256-297 (Wkshp)	297-327 ROH)	327-452 (Wkshp)

User in ROH at the end of Scraping 2

User in ROH for the remainder of the run (16 hours, 28 minutes)

Model Run Time:
0-24 hours
User takes out scrapings after 196 and 452 minutes; emissions truncated.

NMP Scenario G1. Floor, Spray-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 1.26 ACH (= 68 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after each scrape (WINDOWS OPEN)

MCCEM Input Summary

Application Method: Spray-on

Volumes: Workshop volume = 54 m^3

ROH volume = 492 – 54 = 438 m^3

Airflows:

Workshop-outdoors	68 m^3/h
ROH-outdoors	197.1 m^3/h (0.45 ACH)
Workshop-ROH	107 m^3/h

NMP Mass Released:

Floor = 240 sq. ft. surface area

Applied product mass = 19,440 g (Application rate = 81 g/sf)

Overspray = 0.05*19,440 g = 972 g

Total Product Mass = 19,440 + 972 = 20,412 g

Total NMP Mass = 20,412 g × 0.5 (wt. fraction) = 10,206 g

Total NMP mass released (both exponentials) = 10,206 x 0.8695 (release fraction, theoretical) = 8,874.1 g

Mass released per app = 4437.1 g

For each of the 2 applications:

k_1 = 32.83/hr.

% Mass for Exponential 1 = 7.0% of Total mass applied = 0.07/0.8695 = 8% of released NMP

E_{01} = Mass * k_1 = 0.08*4437.1*32.83 = 11,653.6 g/hr. (**NOTE:** only k and Mass are needed as inputs)

k_2 = 0.00237/hr.

% Mass for Exponential 2 = 79.95% of applied NMP = 0.7995/0.8695 = 91.9% of released NMP

E_{02} = Mass * k_2 = 0.919*4437.1*0.00237 = 9.66 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

	Elapsed Time from Time Zero, Minutes (Product User Location)						
Episode	***Apply 1***	***Wait 1***	***Scrape 1***	***Break***	***Apply 2***	***Wait 2***	***Scrape 2***
G1) Floor, Spray-on, Workshop, User in ROH during wait time, 0.45 ACH, 0.5 Weight Fraction, WINDOWS OPEN	0-60 (Wkshp)	60-120 (ROH)	120-210 (Wkshp)	210-270 (ROH)	270-330 (Wkshp)	330-390 (ROH)	390-480 (Wkshp)

User in ROH at the end of Scraping 2

User in ROH for the remainder of the run (16 hours)

Model Run Time:
0-24 hours
User takes out scrapings after 210 and 480 minutes; emissions truncated.

NMP Scenario G2. Floor, Spray-On, Workshop, User in ROH during wait time, ROH=0.45 ACH, Workshop = 0.45 ACH (= 24.3 m^3/hr.), IZ = 107 m^3/hr., 0.5 Weight Fraction, Scrapings removed after each scrape (WINDOWS CLOSED)

MCCEM Input Summary

Application Method: Spray-on

Volumes: Workshop volume = 54 m^3

ROH volume = 492 – 54 = 438 m^3

Airflows:

Workshop-outdoors	24.3 m^3/h
ROH-outdoors	197.1 m^3/h (0.45 ACH)
Workshop-ROH	107 m^3/h

NMP Mass Released:

Floor = 240 sq. ft. surface area

Applied product mass = 19,440 g (Application rate = 81 g/sf)

Overspray = 0.05*19,440 g = 972 g

Total Product Mass = 19,440 + 972 = 20,412 g

Total NMP Mass = 20,412 g × 0.5 (wt. fraction) = 10,206 g

Total NMP mass released (both exponentials) = 10,206g x 0.8695 (release fraction, theoretical) =8,874.1 g

Mass released per app = 4437.1 g

For each of the 2 applications:

k_1 = 32.83/hr.

% Mass for Exponential 1 = 7.0% of Total mass applied = 0.07/0.8695 = 8% of released NMP

E_{01} = Mass * k_1 = 0.08*4437.1*32.83 = 11,653.6 g/hr. (**NOTE:** only k and Mass are needed as inputs)

k_2 = 0.00237/hr.

% Mass for Exponential 2 = 79.95% of applied NMP = 0.7995/0.8695 = 91.9% of released NMP

E_{02} = Mass * k_2 = 0.919*4437.1*0.00237 = 9.66 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

	Elapsed Time from Time Zero, Minutes (Product User Location)						
Episode	***Apply 1***	***Wait 1***	***Scrape 1***	***Break***	***Apply 2***	***Wait 2***	***Scrape 2***
G2) Floor, Spray-on, Workshop, User in ROH during wait time, 0.45 ACH, 0.5 Weight Fraction, WINDOWS CLOSED	0-60 (Wkshp)	60-120 (ROH)	120-210 (Wkshp)	210-270 (ROH)	270-330 (Wkshp)	330-390 (ROH)	390-480 (Wkshp)

User in ROH at the end of Scraping 2

User in ROH for the remainder of the run (16 hours)

Model Run Time:
0-24 hours
User takes out scrapings after 210 and 480 minutes; emissions truncated

NMP Scenario H1. Bathroom, Spray-On, Bathroom + Source Cloud, User in ROH during wait time, ROH=0.18 ACH, Bathroom = 0.18 ACH, IZ (source cloud/bathroom, bathroom/ROH) = 80, 35 m^3/hr., 0.5 Weight Fraction (Csat = 1013 mg/m^3), Scrapings removed after 2nd scrape (WINDOWS CLOSED, 2 applications)

MCCEM Input Summary

MCCEM saturation concentration constraint invoked at 1013 mg/m^3

Application Method: Spray-on

Volumes: Bathroom Volume = 9 m^3 (8 m^3 after subtracting source cloud zone)
Source Cloud Volume = 1 m^3
ROH volume = 492 – 9 = 483 m^3

Airflows:

Bathroom-outdoors	1.6 m^3/h
Source cloud - bathroom	80 m^3/h
Source cloud - outdoors	0
ROH-outdoors	86.9 m^3/h (0.18 ACH)
Bathroom-ROH	35 m^3/h

NMP Mass Released:

Bathtub = 36 sq. ft. surface area
Applied product mass = 2,916 g (Application rate = 81 g/sf)
Overspray = 0.05*2,916 g = 145.8 g
Total Product Mass = 2,916 + 145.8 = 3,061.8 g
Total NMP Mass = 3,061.8 g × 0.5 (wt. fraction) = 1,530.9 g
Total NMP mass released (both exponentials) = 1530.9 x 0.8695 (release fraction, theoretical) =1331.1 g
Mass released per app = 665.6 g

For each of the 2 applications:

k_1 = 32.83/hr.
% Mass for Exponential 1 = 7.0% of Total mass applied = 0.07/0.8695 = 8% of released NMP
E_{01} = Mass * k_1 = 0.08*665.6*32.83 = 1748.1 g/hr. (**NOTE:** only k and Mass are needed as inputs)
k_2 = 0.00237/hr.
% Mass for Exponential 2 = 86.2% of applied NMP = 0.862/0.8695 = 99.2% of released NMP
E_{02} = Mass * k_2 = 0.919*665.6*0.00237 = 1.45 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

Episode	Elapsed Time from Time Zero, Minutes (Product User Location)					
	Apply 1	***Wait 1***	***Scrape 1***	***Apply 2***	***Wait 2***	***Scrape 2***
H1) Bathtub, Spray-On, Bathroom + Source Cloud, User in ROH during wait time, 0.18 ACH, 0.5 Wt. Fract.	0-9 (Src Cloud)	9-39 (ROH)	39-75 (Src Cloud)	75-84 (Src Cloud)	84-114 (ROH)	114-150 (Src Cloud)

User in ROH at the end of Scraping 2
User in ROH for the remainder of the run (21 hours, 30 minutes)

Model Run Time:
0-24 hours
User takes out scrapings after 150 minutes; emissions truncated.

NMP Scenario H2. Bathroom, Spray-On, Bathroom + Source Cloud, User in ROH during wait time, ROH=0.18 ACH, Bathroom = 0.18 ACH, IZ (source cloud/bathroom, bathroom/ROH) = 80, 35 m^3/hr., 0.5 Weight Fraction (Csat = 1013 mg/m^3), Scrapings removed after 2nd and 4th scrapes (WINDOWS CLOSED, 4 applications)

MCCEM Input Summary

MCCEM saturation concentration constraint invoked at 1013 mg/m^3

Application Method: Spray-on

Volumes: Bathroom Volume = 9 m^3 (8 m^3 after subtracting source cloud zone)
Source Cloud Volume = 1 m^3
ROH volume = 492 – 9 = 483 m^3

Airflows:

Bathroom-outdoors	1.6 m^3/h
Source cloud - bathroom	80 m^3/h
Source cloud - outdoors	0
ROH-outdoors	86.9 m^3/h (0.18 ACH)
Bathroom-ROH	35 m^3/h

NMP Mass Released:

Bathtub = 36 sq. ft. surface area
Applied product mass = 2,916 g (Application rate = 81 g/sf)
Overspray = 0.05*2,916 g = 145.8 g
Total Product Mass = 2,916 + 145.8 = 3,061.8 g
Total NMP Mass = 3,061.8 g × 0.5 (wt. fraction) = 1,530.9 g
Total NMP mass released (both exponentials) = 1530.9 x 0.8695 (release fraction, theoretical) =1331.1 g
Mass released per app = 665.6 g

For each of the 2 applications:

k_1 = 32.83/hr.
% Mass for Exponential 1 = 7.0% of Total mass applied = 0.07/0.8695 = 8% of released NMP
E_{01} = Mass * k_1 = 0.08*665.6*32.83 = 1748.1 g/hr. (**NOTE:** only k and Mass are needed as inputs)
k_2 = 0.00237/hr.
% Mass for Exponential 2 = 86.2% of applied NMP = 0.862/0.8695 = 99.2% of released NMP
E_{02} = Mass * k_2 = 0.919*665.6*0.00237 = 1.45 g/hr. (**NOTE:** only k and Mass are needed as inputs)

Application Times and Activity Patterns:

Episode Bathtub, Spray-On, Bathroom + Source Cloud, User in ROH during wait time, 0.18 ACH, 0.5 Wt. Fract	**Elapsed Time from Time Zero, Minutes (Product User Location)**					
	Apply 1 & 3	***Wait 1 & 3***	***Scrape 1 & 3***	***Apply 2 &4***	***Wait 2 &4***	***Scrape 2 &4***
	E2) Bathtub, Brush-On, Bathroom + Source Cloud, User in ROH during wait time, 0.18 ACH, 0.5 Weight Fraction					
1st and 2nd Application	0-9 (Wkshp)	9-39 (ROH)	39-75 (Wkshp)	75-84 (Wkshp)	84-114 (ROH)	114-150 (Wkshp)
3rd and 4th Application	210-219 (Wkshp)	219-249 (ROH)	249-285 (Wkshp)	285-294 (Wkshp)	294-324 (ROH)	324-360 (Wkshp)

User in ROH at the end of Scraping 2 and 4
User in ROH for the remainder of the run (18 hours)

Model Run Time:
0-24 hours
User takes out scrapings after 150 and 360 minutes; emissions truncated.

Appendix B - Spreadsheet: Details of NMP Exposure Model Results

See the separate spreadsheet loaded into this docket (EPA-HQ-OPPT-2016-0231) for the zone-specific and exposure concentrations predicted by MCCEM.

Appendix C - Spreadsheet: NMP Risk Estimation

See the separate spreadsheet loaded into this docket (EPA-HQ-OPPT-2016-0231) for risk calculations.

Appendix D

Table D-1. Eight-hour TWA exposures for additional scenarios

Scenario	Individual	8-Hour TWA exposure	
		mg/m^3	ppm
A1. Coffee Table, Brush Application in Workshop, Windows Open	User	2.2	0.5
	Non-User	1.5	0.4
A2. Coffee Table, Brush Application in Workshop, Windows Closed	User	3.1	0.8
	Non-User	2.2	0.5
B1. Chest, Brush Application in Workshop, Windows Open	User	7.7	1.9
	Non-User	4.3	1.1
B2. Chest, Brush Application in Workshop, Windows Closed	User	10.7	2.6
	Non-User	6.1	1.5

Scenario	Individual	8-Hour TWA exposure	
		mg/m^3	ppm
C1. Dining table and chairs, Brush Application in Workshop, Windows Open	User	70.2	17.3
	Non-User	24.7	6.1
C2. Dining table and chairs, Brush Application in Workshop, Windows Closed	User	97.7	24.1
	Non-User	35.0	8.6
C3. Dining table and chairs, Brush Application in Workshop, Windows Open, Scrapings removed after each scrap	User	54.5	13.4
	Non-User	19.1	4.7
D1. Floors, Roller Application in Workshop, Windows Open	User	110.9	27.4
	Non-User	45.0	11.1
D2. Floors, Roller Application in Workshop, Windows Closed	User	150.6	37.1
	Non-User	63.7	15.7
E1. Bathtub, Brush Application in Bathroom, C_{sat} = 1,013 mg/m^3, 2 Applications	User	78.8	19.4
	Non-User	20.4	5.0
E2. Bathtub, Brush Application in Bathroom, C_{sat} = 1,013 mg/m^3, 4 Applications	User	148.9	36.7
	Non-User	35.7	8.8
F1. Dining table and chairs, Spray Application in Workshop, Windows Open	User	227.1	56.0
	Non-User	94.8	23.4
F2. Dining table and chairs, Spray Application in Workshop, Windows Closed	User	319.3	78.8
	Non-User	133.8	33.0
F3. Dining table and chairs, Spray Application in Workshop, Windows Open	User	218.4	53.9
	Non-User	92.1	22.7
G1. Floors, Spray Application in Workshop, Windows Open	User	540.1	133.2
	Non-User	214.2	52.8
G2. Floors, Spray Application in Workshop, Windows Closed	User	724.6	178.7
	Non-User	303.1	74.8
H1. Bathtub, Spray Application in Bathroom, C_{sat} = 1,013 mg/m^3, 2 Applications	User	339.4	83.7
	Non-User	109.2	26.9
H2. Bathtub, Spray Application in Bathroom, C_{sat} = 1,013 mg/m^3, 4 Applications	User	640.9	158.1
	Non-User	192.8	47.6

915 C_{sat} = Saturation Concentration

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Appendix G ENVIRONMENTAL HAZARDS

EPA has reviewed acceptable ecotoxicity studies for NMP according to the data quality evaluation criteria found in *The Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). The results of these ecotoxicity study evaluations can be found in *NMP (872-50-4) Systematic Review: Supplemental File for the TSCA Risk Evaluation Document*. The data quality evaluation indicated these studies are of high confidence and are used to characterize the environmental hazards of NMP. These studies support that hazard of NMP to aquatic organisms is low and that no further evaluation is required.

The acceptable aquatic studies that were evaluated for NMP are summarized in Table_Apx G-1. The hazard of these studies has been reported (U.S. EPA, 2006b), (OECD, 2007b), (Danish Ministry of the Environment, 2015), (U.S. EPA, 2015) and (Environment Canada, 2017) as stated in the NMP Problem Formulation (U.S. EPA, 2018c).

Table_Apx G-1. On-topic aquatic toxicity studies that were evaluated for N-Methylpyrrolidone

Test Species	Fresh/ Salt Water	Duration	Endpoint	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Fish								
Fathead minnow (*Pimephales promelas*)	Fresh	96-h	LC_{50} = 1072 mg/L	389, 648, 1080, 1800, 3000, 5000 mg/L	Static, Nominal	Mortality	(GAF, 1979)	High
Rainbow trout (*Salmo Gairdneri*)	Fresh	96-h	LC_{50} = 3048 mg/L	778, 1296, 2160, 3600, 6000, 10,000 mg/L	Static, Nominal	Mortality	(GAF, 1979)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	96-h	LC_{50} > 500 mg /L	0, 500 mg/L	Static, Nominal	Mortality	(BASF AG, 1983)	High
Orfe (*Leuciscus idus*)	Fresh	96-h	LC_{50} = 4030 mg/L	100, 215, 464, 1000, 2150, 4640, 10,000 mg/L	Static, Nominal	Mortality	(BASF AG, 1986)	High
Aquatic Invertebrates								
Water flea (*Daphnia magna*)	Fresh	48-h	LC_{50} = 4897 mg/L	389, 648, 1080, 1800, 3000, 5000, 8333 mg/L	Static, Nominal	Mortality	(GAF, 1979)	High
Water flea (*Daphnia magna*)	Fresh	21-day	NOEC=12.5 mg/L LOEC= 25 mg/L	0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50, 100 mg/L	Static, Nominal	Reproduction	(BASF AG, 2001)[a]	High
Grass shrimp (*Palaemonetes vulgaris*)	Salt	96-h	LC_{50}= 1107 mg/L	360, 600, 1000, 1667, 2775 mg/L	Static, Nominal	Mortality	(GAF, 1979)	High
Scud (*Gammarus sp*)	Fresh	96-h	LC_{50}= 4655 mg/L	389, 648, 1080, 1800, 3000, 5000, 8333 mg/L	Static, Nominal	Mortality	(GAF, 1979)	High
Mud crabs (*Neopanope texana sayi*)	Salt	96-h	LC_{50}= 1585 mg/L	360, 600, 1000, 1667, 2775 mg/L	Static, Nominal	Mortality	(GAF, 1979)	High
Algae								

Test Species	Fresh/ Salt Water	Duration	Endpoint	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Algae (*Scenedemus subspicatus*)	Fresh	72-h	E_bC_{50}=600 ErC_{50}=673 mg/L	7.8, 15.6, 31.3, 62.5, 125, 250, 500 mg/L	Static, Nominal	Biomass Growth rate	(BASF AG, 1989)	High
Algae (*Scenedemus subspicatus*)	Fresh	72-h	LOEC=250 NOEC=125	7.8, 15.6, 31.3, 62.5, 125, 250, 500 mg/L	Static, Nominal	Growth	(BASF AG, 1989)	High

[a] Reservation of Rights: BASF has agreed to share this toxicity study report ("Study Report") with US EPA, at its written request, for EPA 's use in implementing a statutory requirement of the Toxic Substances Control Act ("TSCA "). Every other use, exploitation, reproduction, distribution, publication or submission to any other party requires BASF's written permission, except as otherwise provided by law. The submission of this Study Report to a public docket maintained by the United States Environmental Protection Agency is not a waiver of BASF's ownership rights. No consent is granted for any other third-party use of this Study Report for any purpose, in any jurisdiction. Specifically, and by example, no consent is granted allowing the use of this Study Report by a private entity in requesting any regulatory status, registration or other approval or benefit, whether international, national, state or local, including but not limited to the Regulation Evaluation Authorization and Restriction of Chemicals ("REACH") regulation administered by European Chemicals Agency ("ECHA"), an agency of the European Union.

Appendix H HUMAN HEALTH HAZARDS

H.1 Hazard and Data Evaluation Summaries

H.1.1 Hazard and Data Evaluation Summary for Acute and Short-term Oral Exposure Studies

Table_Apx H-1. Hazard and Data Evaluation Summary for Acute and Short-term Oral Exposure Studies

Target Organ/ System	Study Type	Species, Strain, Sex (Number/group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	Effect	Reference	Data Quality Evaluation
Body Weight	Short-term (1-30 days)	Rat, Other, Male (5)	0, 149, 429, 1234, 2019 mg/kg-bw/day (0, 2000, 6000, 18,000, and 30,000 ppm)	4 weeks	NOAEL = 429 mg/kg - bw/day	NOAEL = 429 mg/kg - bw/day	Decreased body weight and altered testes and liver weights were observed at 1234 mg/kg-bw/day and above. Degeneration/atrophy of testicular seminiferous tubules were observed 1/5 males at 1234 mg/kg-bw/day and in 5/5 at 2019 mg/kg-bw/day. Increased incidence of centrilobular hepatocellular hypertrophy and decreased serum glucose were observed at 1234 mg/kg-bw/day and above.	Malek et al (1997)	High

Target Organ/ System	Study Type	Species, Strain, Sex (Number/group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	Effect	Reference	Data Quality Evaluation
Body Weight	Short-term (1-30 days)	Rat, Other Female (5)	0, 161, 493, 1548, 2268 mg/kg-bw/day (0, 2000, 6000, 18,000, and 30,000 ppm)	4 weeks	NOAEL = 1548 mg/kg - bw/day	NOAEL = 1548 mg/kg - bw/day	Decreased body weight and body weight gain were observed at 2268 mg/kg-bw/day. Increased serum total protein, albumin, and cholesterol levels and increased incidence of centrilobular hepatocellular hypertrophy, hypocellular bone marrow, and thymic atrophy were also observed at 2268 mg/kg-bw/day.	Malek et al (1997)	High
Body Weight	Short-term (1-30 days)	Mouse, B6C3F1, Female (5)	0, 180, 920, 2970, 4060 mg/kg-bw/day (0, 500, 2500. 7500, 10,000 ppm)	4 weeks	Not Reported	NOAEL = 4060 mg/kg - bw/day	No exposure-related effects	NMP Producers Group (1994)	High
Body Weight	Short-term (1-30 days)	Mouse B6C3F1, Male (5)	0, 130, 720, 2130, 2670 mg/kg-bw/day (0, 500, 2500. 7500, 10,000 ppm)	4 weeks	Not Reported	NOAEL = 2670 mg/kg - bw/day	No exposure-related effects	NMP Producers Group (1994)	High
Clinical Chemistry/ Biochemical	Short-term (1-30 days)	Rat Sprague-Dawley, Male (5)	0, 250, 500, 1000 mg/kg-bw/day	5 days/ week for 5 weeks	Not Reported	NOAEL = 250 mg/kg - bw/day	Decreased serum creatinine	Gopinathan et al (2013)	Medium

Target Organ/ System	Study Type	Species, Strain, Sex (Number/group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	Effect	Reference	Data Quality Evaluation
Endocrine	Short-term (1-30 days)	Rat, Other, Female (5)	0, 161, 493, 1548, 2268 mg/kg-bw/day (0, 2000, 6000, 18000, and 30000 ppm)	4 weeks	NOAEL = 1548 mg/kg - bw/day	NOAEL = 1548 mg/kg - bw/day	Decreased body weight and body weight gain were observed at 2268 mg/kg-bw/day. Increased serum total protein, albumin, and cholesterol levels and increased incidence of centrilobular hepatocellular hypertrophy, hypocellular bone marrow, and thymic atrophy were also observed at 2268 mg/kg-bw/day.	Malek et al (1997)	High
Hemato-logical and Immune	Short-term (1-30 days)	Rat, Sprague-Dawley, Male (5)	0, 250, 500, 1000 mg/kg-bw/day	5 days/ week for 5 weeks	Not Reported	NOAEL = 1000 mg/kg - bw/day	No mortalities occurred and no changes were reported for hematology parameters or liver or spleen weights.	Gopinathan et al (2013)	Medium
Hepatic	Short-term (1-30 days)	Rat, Sprague-Dawley, Male (5)	0, 250, 500, 1000 mg/kg-bw/day	5 days/ week for 5 weeks	Not Reported	NOAEL = 1000 mg/kg - bw/day	No mortalities occurred and no changes were reported for hematology parameters or liver or spleen weights.	Gopinathan et al (2013)	Medium

Target Organ/ System	Study Type	Species, Strain, Sex (Number/group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	Effect	Reference	Data Quality Evaluation
Hepatic	Short-term (1-30 days)	Rat, Other Female (5)	0, 161, 493, 1548, 2268 mg/kg-bw/day (0, 2000, 6000, 18,000, and 30,000 ppm)	4 weeks	NOAEL = 1548 mg/kg - bw/day	NOAEL = 1548 mg/kg - bw/day	Decreased body weight and body weight gain were observed at 2268 mg/kg-bw/day. Increased serum total protein, albumin, and cholesterol levels and increased incidence of centrilobular hepatocellular hypertrophy, hypocellular bone marrow, and thymic atrophy were also observed at 2268 mg/kg-bw/day.	Malek et al (1997)	High
Hepatic	Short-term (1-30 days)	Mouse, B6C3F1, Female (5)	0, 180, 920, 2970, 4060 mg/kg-bw/day (0, 500, 2500. 7500, 10,000 ppm)	4 weeks	Not Reported	NOAEL = 4060 mg/kg - bw/day	No exposure-related effects	NMP Producers Group (1994)	High
Hepatic	Short-term (1-30 days)	Mouse, B6C3F1, Male (5)	0, 130, 720, 2130, 2670 mg/kg-bw/day (0, 500, 2500. 7500, 10,000 ppm)	4 weeks	Not Reported	NOAEL = 2670 mg/kg - bw/day	No exposure-related effects	NMP Producers Group (1994)	High
Mortality	Short-term (1-30 days)	Rat, Sprague-Dawley, Male (5)	0, 250, 500, 1000 mg/kg-bw/day	5 days/ week for 5 weeks	Not Reported	NOAEL = 1000 mg/kg - bw/day	No mortalities occurred and no changes were reported for hematology parameters or liver or spleen weights.	Gopinathan et al (2013)	Medium

Target Organ/ System	Study Type	Species, Strain, Sex (Number/group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	Effect	Reference	Data Quality Evaluation
Mortality	Short-term (1-30 days)	Mouse, B6C3F1, Male (5)	0, 130, 720, 2130, 2670 mg/kg-bw/day (0, 500, 2500, 7500, 10000 ppm)	4 weeks	NOAEL = 0.048	NOAEL = 1125 mg/kg - bw/day	Mortality in a male mouse that also showed renal effects. death was considered related to treatment.	Malek et al (1997)	High
Mortality	Short-term (1-30 days)	Mouse, B6C3F1, Female (5)	0, 180, 920, 2970, 4060 mg/kg-bw/day (0, 500, 2500. 7500, 10,000 ppm)	4 weeks	Not Reported	NOAEL = 4060 mg/kg - bw/day	No exposure-related effects	NMP Producers Group (1994)	High
Mortality	Short-term (1-30 days)	Mouse, B6C3F1, Male (5)	0, 130, 720, 2130, 2670 mg/kg-bw/day (0, 500, 2500. 7500, 10,000 ppm)	4 weeks	Not Reported	NOAEL = 2670 mg/kg - bw/day	No exposure-related effects	NMP Producers Group (1994)	High
Not Reported	Short-term (1-30 days)	Rat, Sprague-Dawley, Male (5)	0, 250, 500, 1000 mg/kg-bw/day	5 days/ week for 5 weeks	Not Reported	NOAEL = 250 mg/kg - bw/day	Decreased serum creatinine	Gopinathan et al (2013)	Medium
Not Reported	Short-term (1-30 days)	Rat, Sprague-Dawley, Male (5)	0, 250, 500, 1000 mg/kg-bw/day	5 days/ week for 5 weeks	Not Reported	NOAEL = 250 mg/kg - bw/day	Decreased serum creatinine	Gopinathan et al (2013)	Medium

Target Organ/ System	Study Type	Species, Strain, Sex (Number/group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	Effect	Reference	Data Quality Evaluation
Renal	Short-term (1-30 days)	Rat, Sprague-Dawley, Male (5)	0, 250, 500, 1000 mg/kg-bw/day	5 days/ week for 5 weeks	Not Reported	Not Reported	Mottled kidneys were reported bilaterally with a combined incidence in all dose groups (250, 500, and 1000 mg/kg-bw/day) of 8/15. This was not observed in controls. No changes were reported for urine chemistry parameters or kidney weights. Incidences of mottled kidneys for each dose group were not reported, so I did not assign a NOAEL or LOAEL for renal effects.	Gopinathan et al (2013)	Medium
Renal	Short-term (1-30 days)	Mouse, B6C3F1, Female (5)	0, 180, 920, 2970, 4060 mg/kg-bw/day (0, 500, 2500. 7500, 10,000 ppm)	4 weeks	NOAEL = 920 mg/kg - bw/day	NOAEL = 920 mg/kg - bw/day	Dark yellow urine in all animals at Dose 3, 4, and 5. Cloudy swelling of the distal renal tubule in 3/5 females at Dose 5	NMP Producers Group (1994)	High
Renal	Short-term (1-30 days)	Mouse, B6C3F1, Male (5)	0, 130, 720, 2130, 2670 mg/kg-bw/day (0, 500, 2500. 7500, 10,000 ppm)	4 weeks	NOAEL = 720 mg/kg - bw/day	NOAEL = 720 mg/kg - bw/day	Dark yellow urine in all animals at Dose 3, 4, and 5. Cloudy swelling of the distal renal tubule in 2/5 males at Dose 4. and 4/5 males at Dose 5	NMP Producers Group (1994)	High

H.1.2 Hazard and Data Evaluation Summary for Reproductive and Developmental Oral Exposure Studies

Table_Apx H-2. Hazard and Data Evaluation Summary for Reproductive and Developmental Oral Exposure Studies

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concen-trations	Duration	Author Reported Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	Effect Measured	Reference	Data Quality Evaluation
Body Weight	Repro-ductive	Rat, Male (22-24)	0, 100, 300, 1000 mg/kg-bw/day	5 days/ week for 10 weeks prior to mating and 1 week during mating	Not Reported	NOAEL = 300 mg/kg - bw/day	Body weight decrement of at least 10%	Sitarek et al (2008)	High
Growth and Develop-ment	Repro-ductive	Rat, Other, Male (22-24)	0, 100, 300, 1000 mg/kg-bw/day	5 days/ week for 10 weeks prior to mating and 1 week during mating	Not Reported	NOAEL = 100 mg/kg - bw/day	Decreased offspring viability through PND4	Sitarek et al (2008)	High

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concen-trations	Duration	Author Reported Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	Effect Measured	Reference	Data Quality Evaluation
Growth and Develop-ment	Repro-ductive	Rat, Wistar, Female (22-28)	0, 150, 450, 1000 mg/kg-bw/day	5 days/ week for two weeks before mating, during gestation and lactation	LOAEL = 150 mg/kg-bw/day	LOAEL = 150 mg/kg-bw/day	Significant decrease in pup survival within three weeks of birth at all doses.	Sitarek et al (2012)	High
Repro-ductive	Subchronic (30-90 days)	Dog, Beagle, Both (6/sex)	0, 24, 75, 246 mg/kg-bw/day in males; 0, 24, 76, 246 mg/kg-bw/day in females (actual concentratio ns)	13 weeks	Not Reported	NOAEL = 246 mg/kg -bw/day	No effects on reproductive organs, hematological/ immune, body weight, relative organ (liver, kidney, spleen, heart, thyroid, adrenal glands, brain, and pituitary) weights.	Becci et al (1983)	High

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concen-trations	Duration	Author Reported Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	Effect Measured	Reference	Data Quality Evaluation
Repro-ductive	Short-term (1-30 days)	Rat, Other, Male (5)	0, 149, 429, 1234, 2019 mg/kg-bw/day (0, 2000, 6000, 18,000, 30,000 ppm)	4 weeks	NOAEL = 429 mg/kg - bw/day	NOAEL = 429 mg/kg - bw/day	Decreased body weight and altered testes and liver weights were observed at 1234 mg/kg-bw/day and above. Degeneration/atrophy of testicular seminiferous tubules were observed 1/5 males at 1234 mg/kg-bw/day and in 5/5 at 2019 mg/kg-bw/day. Increased incidence of centrilobular hepatocellular hypertrophy and decreased serum glucose were observed at 1234 mg/kg-bw/day and above.	Malek et al (1997)	High
Repro-ductive	Subchronic (30-90 days)	Rat, Other, Male (10)	1, 169, 433, 1057 mg/kg-bw/day (0, 3000, 7500, 18,000 ppm)	90 days	Not Reported	NOAEL = 1057 mg/kg - bw/day	No adverse effects.	Malley et al (1999)	High

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concen-trations	Duration	Author Reported Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	Effect Measured	Reference	Data Quality Evaluation
Repro-ductive	Subchronic (30-90 days)	Mouse, Both (20/sex)	0, 277, 619, 1931 mg/kg-bw/day (0, 1000, 2500, 7500 ppm)	90 days	Not Reported	NOAEL = 1931 mg/kg - bw/day	No adverse effects.	Malley et al (1999)	High
Repro-ductive	Chronic (>90 days)	Rat, Other, Male (62)	0, 66.4, 207, 678 mg/kg-bw/day (0, 1600, 5000, 15,000 ppm)	2 years	Not Reported	NOAEL = 207 mg/kg - bw/day	Biliateral degeneration/atrophy of seminiferous tubules in the tests, bilateral oligospermia/germ cell debris in the epididymites, centrilobular fatty change in the liver	Malley et al (2001)	High
Repro-ductive	Chronic (>90 days)	Rat, Other, Female (62)	0, 87.8, 283, 939 mg/kg-bw/day (0, 1600, 5000, 15,000 ppm)	2 years	Not Reported	NOAEL = 939 mg/kg - bw/day	No exposure-related adverse effects	Malley et al (2001)	High
Repro-ductive	Chronic (>90 days)	Mouse, B6C3F1, Male (50)	0, 89, 173, 1089 mg/kg-bw/day (0, 600, 1200, 7200 ppm)	18 months	Not Reported	NOAEL = 1089 mg/kg - bw/day	No adverse effects	Malley et al (2001)	High

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concen-trations	Duration	Author Reported Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	Effect Measured	Reference	Data Quality Evaluation
Repro-ductive	Chronic (>90 days)	Mouse, B6C3F1, Female (50)	0, 115, 221, 1399 mg/kg-bw/day (0, 600, 1200, 7200 ppm)	18 months	Not Reported	NOAEL = 1399 mg/kg - bw/day	No adverse effects	Malley et al (2001)	High
Repro-ductive	Repro-ductive	Rat, Other, Male (22-24)	0, 100, 300, 1000 mg/kg-bw/day	5 days/ week	Not Reported	NOAEL = 100 mg/kg - bw/day	Decreased offspring viability through PND4	Sitarek et al (2008)	High
Repro-ductive	Short-term (1-30 days)	Mouse, B6C3F1, Male (5)	0, 130, 720, 2130, 2670 mg/kg-bw/day (0, 500, 2500. 7500, 10,000 ppm)	4 weeks	Not Reported	NOAEL = 2670 mg/kg - bw/day	No exposure-related effects	NMP Producers Group/ BASF (1994)	High
Repro-ductive	Repro-ductive	Rat, Wistar, Female (22-28)	0, 150, 450, 1000 mg/kg-bw/day	5 days/ week for two weeks before mating, during gestation and lactation	NOAEL = 150 mg/kg-bw/day	NOAEL = 150 mg/kg-bw/day	Significantly decreased female fertility index	Sitarek et al (2012)	High

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concen-trations	Duration	Author Reported Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	Effect Measured	Reference	Data Quality Evaluation
Thyroid	Repro-ductive	Rat , Male, (22-24)	0, 100, 300, 1000 mg/kg-bw/day	5 days/ week for 10 weeks prior to mating and 1 week during mating	Not Reported	NOAEL = 300 mg/kg -bw/day	Significantly increased absolute and relative thyroid weight.	Sitarek et al (2008)	High

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H.1.3 Hazard and Data Evaluation Summary for Reproductive and Developmental Inhalation Exposure Studies

Table_Apx H-3. Hazard and Data Evaluation Summary for Reproductive and Developmental Inhalation Exposure Studies

Target Organ/ System	Study Type	Species, Strain, Sex (Number /group)	Doses/ Concen-trations	Duration	Author Reported Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	Effect Measured	Reference	Data Quality Evaluation
Body Weight	Developmental	Rat, Sprague-Dawley, Female (25-26)	0, 122, 243, 487 mg/m^3	6 hours/ day 7 days/ week for 15 weeks	NOAEL = 122 mg/m^3	NOAEL = 122 mg/m^3	LOAEL for decreased maternal weight gain at 243 mg/m^3. Maternal food intake also decreased at 487 mg/m^{3+}.	Saillenfait et al (2003)	High
Growth and Development	Reproductive	Rat, Other, Both (10M and 20F)	0, 42, 206, 472 mg/m^3	6 hours/ day 7 days/ week for 143 weeks	Not Reported	NOAEL = 42 mg/m^3	Decreased F1 offspring weights per litter from PND 1 to PND 21, and decreased fetal body weight in developmental phase of study, at highest dose. F0 dams exhibited decreased response to auditory stimuli at the highest dose.	Solomon et al (1995)	High

Target Organ/ System	Study Type	Species, Strain, Sex (Number /group)	Doses/ Concen-trations	Duration	Author Reported Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	Effect Measured	Reference	Data Quality Evaluation
Growth and Development	Developmental	Rat, Other, Female (25)	0, 100, 360 mg/m^3	6 hours/ day 7 days/ week for 10 weeks	Not Reported	NOAEL = 360 mg/m^3	No effects on uterine or litter parameters, fetal weight or length, or incidence of gross, soft tissue, or skeletal anomalies	Lee et al (1987)	High
Neuro-logical/ Behavior	Reproductive	Rat, Other, Both (10M and 20F)	0, 42, 206, 472 mg/m^3	6 hours/ day 7 days/ week for 143 weeks	Not Reported	NOAEL = 42 mg/m^3	Decreased F1 offspring weights per litter from PND 1 to PND 21, and decreased fetal body weight in developmental phase of study, at highest dose. F0 dams exhibited decreased response to auditory stimuli at the highest dose.	Solomon et al (1995)	High

Target Organ/ System	Study Type	Species, Strain, Sex (Number /group)	Doses/ Concen-trations	Duration	Author Reported Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concen-tration (NOAEL, LOAEL, LC50) (Sex)	Effect Measured	Reference	Data Quality Evaluation
Repro-ductive	Reproductive	Rat, Other, Both (10M and 20F)	0, 42, 206, 472 mg/m^3	6 hours/ day 7 days/ week for 143 weeks	NOAEL = 472 mg/m^3	NOAEL = 472 mg/m^3	No significant difference in reproductive performance or adult body weight. Study notes condensation on inside of high dose chambers, which precluded achieving target concentration of 527 mg/m^3.	Solomon et al (1995)	High
Repro-ductive	Chronic (>90 days)	Rat, Crj: CD(SD), Both (120)	0, 41, 405 mg/m^3	6 hours/ day 5 days/ week	Not Reported	NOAEL = 41 mg/m^3	Mammary gland hyperplasia	DuPont (1982)	Medium
Repro-ductive	Chronic (>90 days)	Rat, Crj: CD(SD), Both (120)	0, 41, 405 mg/m^3	6 hours/ day 5 days/ week	Not Reported	NOAEL = 405 mg/m^3	No adverse effects (based on histopathology of epididymites and prostate)	DuPont (1982)	Medium

H.1.4 Hazard and Data Evaluation Summary for Reproductive and Developmental Dermal Exposure Studies

Table_Apx H-4. Hazard and Data Evaluation Summary for Reproductive and Developmental Dermal Exposure Studies

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Concentration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concentration (NOAEL, LOAEL, LC50) (Sex)	Effect Measured	Reference	Data Quality Evaluation
Growth and development	Developmental	Sprague-Dawley, Female (25)	75, 237 and 750 mg/kg-bw/day	Days 6-15 of gestation		NOAEL= 237 mg/kg-bw/day	Decreased number of live fetuses per dam and increased percentage of resorption sites and skeletal abnormalities as well as maternal toxicity indicated by reduced body weight gain at the highest dose;	Becci et al (1982)	Medium

H.1.5 Hazard and Data Evaluation Summary for Sub-chronic and Chronic Non-cancer Inhalation Exposure Studies

Table_Apx H-5. Hazard and Data Evaluation Summary for Sub-chronic and Chronic Non-cancer Inhalation Exposure Studies

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Concentration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concentration (NOAEL, LOAEL, LC50) (Sex)	Effect Measured	Reference	Data Quality Evaluation
Body Weight	Chronic (>90 days)	Rat, Crj: CD(SD), Both (120)	0, 41, 405 mg/m^3	6 hours/ day 5 days/week	Not Reported	NOAEL = 405 mg/m^3	Body weight was significantly decreased in 405 mg/m^3 males (but only 6% lower than controls). Effects on mortality, hematology and clinical chemistry parameters, the kidney, and cancer incidence were not temporally- and/or concentration-related, and/or were not toxicologically relevant (e.g., decreased cancer incidence).	DuPont (1982)	Medium

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Concentration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concentration (NOAEL, LOAEL, LC50) (Sex)	Effect Measured	Reference	Data Quality Evaluation
Clinical Chem-istry/ Biochem-ical	Chronic (>90 days)	Rat, Crj: CD(SD), Both (120)	0, 41, 405 mg/m^3	6 hours/ day 5 days/week	Not Reported	NOAEL = 405 mg/m^3	Body weight was significantly decreased in 405 mg/m^3 males (but only 6% lower than controls). Effects on mortality, hematology and clinical chemistry parameters, the kidney, and cancer incidence were not temporally- and/or concentration-related, and/or were not toxicologically relevant (e.g., decreased cancer incidence).	DuPont (1982)	Medium

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Concentration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concentration (NOAEL, LOAEL, LC50) (Sex)	Effect Measured	Reference	Data Quality Evaluation
Hemato-logical and Immune	Chronic (>90 days)	Rat, Crj: CD(SD), Both (120)	0, 41, 405 mg/m^3	6 hours/ day 5 days/week	Not Reported	NOAEL = 405 mg/m^3	Body weight was significantly decreased in 405 mg/m^3 males (but only 6% lower than controls). Effects on mortality, hematology and clinical chemistry parameters, the kidney, and cancer incidence were not temporally- and/or concentration-related, and/or were not toxicologically relevant (e.g., decreased cancer incidence).	DuPont (1982)	Medium

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Concentration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concentration (NOAEL, LOAEL, LC50) (Sex)	Effect Measured	Reference	Data Quality Evaluation
Mortality	Chronic (>90 days)	Rat, Crj: CD(SD), Both (120)	0, 41, 405 mg/m^3	6 hours/ day 5 days/week	Not Reported	NOAEL = 405 mg/m^3	Body weight was significantly decreased in 405 mg/m^3 males (but only 6% lower than controls). Effects on mortality, hematology and clinical chemistry parameters, the kidney, and cancer incidence were not temporally- and/or concentration-related, and/or were not toxicologically relevant (e.g., decreased cancer incidence).	DuPont (1982)	Medium

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Concentration (NOAEL, LOAEL, LC50) (Sex)	EPA Identified Effect Dose or Concentration (NOAEL, LOAEL, LC50) (Sex)	Effect Measured	Reference	Data Quality Evaluation
Not Reported	Chronic (>90 days)	Rat, Crj: CD(SD), Both (120)	0, 41, 405 mg/m^3	6 hours/ day 5 days/week	Not Reported	NOAEL = 405 mg/m^3	Body weight was significantly decreased in 405 mg/m^3 males (but only 6% lower than controls). Effects on mortality, hematology and clinical chemistry parameters, the kidney, and cancer incidence were not temporally- and/or concentration-related, and/or were not toxicologically relevant (e.g., decreased cancer incidence).	DuPont (1982)	Medium

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H.1.6 Hazard and Data Evaluation Summary for Sub-chronic and Chronic Non-cancer Oral Exposure Studies

Table_Apx H-6. Hazard and Data Evaluation Summary for Sub-chronic and Chronic Non-cancer Oral Exposure Studies

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Conc. (NOAEL, LOAEL, LC_{50})	EPA Identified Effect Dose or Conc. (NOAEL, LOAEL, LC_{50})	Effect Measured	Reference	Data Quality Evaluation
Body Weight	Sub-chronic (30-90 days)	Mouse, Both (20/sex)	0, 277, 619, 1931 mg/kg-bw/day (0, 1000, 2500, 7500 ppm)	90 days	Not Reported	NOAEL = 1931 mg/kg - bw/day	No adverse effects.	Malley et al (1999)	High
Body Weight	Sub-chronic (30-90 days)	Rat, Other, Male (20-26)	1, 169, 433, 1057 mg/kg-bw/day (0, 3000, 7500, 18,000 ppm)	90 days	NOAEL = 0.048	NOAEL = 1057 mg/kg - bw/day	Body weight effects not considered adverse (associated with decreased food consumption, indicating palatability issue)	Malley et al (1999)	High
Body Weight	Sub-chronic (30-90 days)	Rat, Other, Female (20-26)	0, 217, 565, 1344 mg/kg-bw/day (0, 3000, 7500, 18,000 ppm)	90 days	NOAEL = 0.048	NOAEL = 1344 mg/kg - bw/day	Body weight effects within 10% of control	Malley et al (1999)	High
Body Weight	Chronic (>90 days)	Rat, Other, Male (62)	0, 66.4, 207, 678 mg/kg-bw/day (0, 1600, 5000, 15,000 ppm)	2 years	NOAEL = 207 mg/kg - bw/day	NOAEL = 207 mg/kg - bw/day	Study authors report a study NOAEL of 207 mg/kg/day in male rats based on 25% decrease in terminal body weight and increased incidence of severe chronic progressive nephropathy.	Malley et al (2001)	High

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Conc. (NOAEL, LOAEL, LC_{50})	EPA Identified Effect Dose or Conc. (NOAEL, LOAEL, LC_{50})	Effect Measured	Reference	Data Quality Evaluation
Body Weight	Chronic (>90 days)	Rat, Other, Female (62)	0, 87.8, 283, 939 mg/kg-bw/day (0, 1600, 5000, 15,000 ppm)	2 years	NOAEL = 283 mg/kg - bw/day	NOAEL = 283 mg/kg - bw/day	Study authors report a study NOAEL of 283 mg/kg/day in female rats based on 35% decrease in terminal body weight.	Malley et al (2001)	High
Body Weight	Chronic (>90 days)	Mouse, B6C3F1, Male (50)	0, 89, 173, 1089 mg/kg-bw/day (0, 600, 1200, 7200 ppm)	18 months	Not Reported	NOAEL = 1089 mg/kg - bw/day	No adverse effects	Malley et al (2001)	High
Body Weight	Chronic (>90 days)	Mouse, B6C3F1, Female (50)	0, 115, 221, 1399 mg/kg-bw/day (0, 600, 1200, 7200 ppm)	18 months	Not Reported	NOAEL = 1399 mg/kg - bw/day	No adverse effects	Malley et al (2001)	High
Hematological and Immune	Sub-chronic (30-90 days)	Dog, Beagle Both (6/sex)	0, 24, 75, 246 mg/kg-bw/day in males; 0, 24, 76, 246 mg/kg-bw/day in females	13 weeks	Not Reported	NOAEL = 246 mg/kg - bw/day	No effects on reproductive organs, hematological/immune , body weight, relative organ (liver, kidney, spleen, heart, thyroid, adrenal glands, brain, and pituitary) weights.	Becci et al (1983)	High
Hepatic	Sub-chronic (30-90 days)	Rat, Other, Male (10)	1, 169, 433, 1057 mg/kg-bw/day (0, 3000, 7500, 18,000 ppm)	90 days	Not Reported	NOAEL = 1057 mg/kg - bw/day	No adverse effects.	Malley et al (1999)	High

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Conc. (NOAEL, LOAEL, LC_{50})	EPA Identified Effect Dose or Conc. (NOAEL, LOAEL, LC_{50})	Effect Measured	Reference	Data Quality Evaluation
Hepatic	Sub-chronic (30-90 days)	Rat, Other, Female (20-26)	0, 217, 565, 1344 mg/kg-bw/day (0, 3000, 7500, 18,000 ppm)	90 days	Not Reported	NOAEL = 1344 mg/kg - bw/day	No adverse effects.	Malley et al (1999)	High
Hepatic	Sub-chronic (30-90 days)	Mouse, Both (20/sex)	0, 277, 619, 1931 mg/kg-bw/day (0, 1000, 2500, 7500 ppm)	90 days	Not Reported	NOAEL = 1931 mg/kg - bw/day	No adverse effects.	Malley et al (1999)	High
Hepatic	Chronic (>90 days)	Rat, Other, Male (62)	0, 66.4, 207, 678 mg/kg-bw/day (0, 1600, 5000, 15,000 ppm)	2 years	Not Reported	NOAEL = 207 mg/kg - bw/day	Biliateral degeneration/atrophy of seminiferous tubules in the tests, bilateral oligospermia/germ cell debris in the epididymites, centrilobular fatty change in the liver	Malley et al (2001)	High
Hepatic	Chronic (>90 days)	Rat, Other, Female (62)	0, 87.8, 283, 939 mg/kg-bw/day (0, 1600, 5000, 15,000 ppm)	2 years	Not Reported	NOAEL = 939 mg/kg - bw/day	No exposure-related adverse effects	Malley et al (2001)	High

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Conc. (NOAEL, LOAEL, LC_{50})	EPA Identified Effect Dose or Conc. (NOAEL, LOAEL, LC_{50})	Effect Measured	Reference	Data Quality Evaluation
Hepatic	Chronic (>90 days)	Mouse, B6C3F1, Female (50)	0, 115, 221, 1399 mg/kg-bw/day (0, 600, 1200, 7200 ppm)	18 months	NOAEL = 221 mg/kg - bw/day	NOAEL = 221 mg/kg - bw/day	Study authors reported a study NOAEL of 221 mg/kg/day for female mice based on increased liver weight, increased incidence of hepatocellular basophilic foci, eosinophilic foci, and cellular alterations in liver, and increased hepatocellular adenoma and carcinoma.	Malley et al (2001)	High
Hepatic	Chronic (>90 days)	Mouse, B6C3F1, Male (50)	0, 89, 173, 1089 mg/kg-bw/day (0, 600, 1200, 7200 ppm)	18 months	NOAEL = 89 mg/kg - bw/day	NOAEL = 89 mg/kg - bw/day	Study authors report a study NOAEL of 89 mg/kg/day in male mice based on increased liver weight in the mid- and high-dose groups. At the high dose, additional effects included increased incidence of hepatocellular hypertrophy, clear cell foci, eosinophilic foci, and cellular alterations in the liver.	Malley et al (2001)	High
Mortality	Sub-chronic (30-90 days)	Rat, Other, Male (10)	1, 169, 433, 1057 mg/kg-bw/day (0, 3000, 7500, 18,000 ppm)	90 days	Not Reported	NOAEL = 1057 mg/kg - bw/day	No adverse effects.	Malley et al (1999)	High

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Conc. (NOAEL, LOAEL, LC_{50})	EPA Identified Effect Dose or Conc. (NOAEL, LOAEL, LC_{50})	Effect Measured	Reference	Data Quality Evaluation
Mortality	Sub-chronic (30-90 days)	Rat, Other, Female (20-26)	0, 217, 565, 1344 mg/kg-bw/day (0, 3000, 7500, 18,000 ppm)	90 days	Not Reported	NOAEL = 1344 mg/kg - bw/day	No adverse effects.	Malley et al (1999)	High
Mortality	Sub-chronic (30-90 days)	Mouse, Both (20/sex)	0, 277, 619, 1931 mg/kg-bw/day (0, 1000, 2500, 7500 ppm)	90 days	Not Reported	NOAEL = 1931 mg/kg - bw/day	No adverse effects.	Malley et al (1999)	High
Mortality	Chronic (>90 days)	Rat, Other, Male (62)	0, 66.4, 207, 678 mg/kg-bw/day (0, 1600, 5000, 15,000 ppm)	2 years	NOAEL = 0.048	NOAEL = 66.4 mg/kg - bw/day	Decreased survival at 207 mg/kg/day (21%) compared with control (32%)	Malley et al (2001)	High
Mortality	Chronic (>90 days)	Rat, Other, Female (62)	0, 87.8, 283, 939 mg/kg-bw/day (0, 1600, 5000, 15,000 ppm)	2 years	Not Reported	NOAEL = 939 mg/kg - bw/day	No exposure-related adverse effects	Malley et al (2001)	High
Mortality	Chronic (>90 days)	Mouse, B6C3F1, Male (50)	0, 89, 173, 1089 mg/kg-bw/day (0, 600, 1200, 7200 ppm)	18 months	Not Reported	NOAEL = 1089 mg/kg - bw/day	No adverse effects	Malley et al (2001)	High
Mortality	Chronic (>90 days)	Mouse, B6C3F1, Female (50)	0, 115, 221, 1399 mg/kg-bw/day (0, 600, 1200, 7200 ppm)	18 months	Not Reported	NOAEL = 1399 mg/kg - bw/day	No adverse effects	Malley et al (2001)	High

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Conc. (NOAEL, LOAEL, LC_{50})	EPA Identified Effect Dose or Conc. (NOAEL, LOAEL, LC_{50})	Effect Measured	Reference	Data Quality Evaluation
Renal	Sub-chronic (30-90 days)	Rat, Other, Male (10)	1, 169, 433, 1057 mg/kg-bw/day (0, 3000, 7500, 18,000 ppm)	90 days	Not Reported	NOAEL = 1057 mg/kg - bw/day	No adverse effects.	Malley et al (1999)	High
Renal	Sub-chronic (30-90 days)	Rat, Other, Female (20-26)	0, 217, 565, 1344 mg/kg-bw/day (0, 3000, 7500, 18,000 ppm)	90 days	Not Reported	NOAEL = 1344 mg/kg - bw/day	No adverse effects.	Malley et al (1999)	High
Renal	Sub-chronic (30-90 days)	Mouse, Both (20/sex)	0, 277, 619, 1931 mg/kg-bw/day (0, 1000, 2500, 7500 ppm)	90 days	Not Reported	NOAEL = 1931 mg/kg - bw/day	No adverse effects.	Malley et al (1999)	High
Renal	Chronic (>90 days)	Rat, Other, Male (62)	0, 66.4, 207, 678 mg/kg-bw/day (0, 1600, 5000, 15,000 ppm)	2 years	NOAEL = 207 mg/kg - bw/day	NOAEL = 207 mg/kg - bw/day	Study authors report a study NOAEL of 207 mg/kg/day in male rats based on 25% decrease in terminal body weight and increased incidence of severe chronic progressive nephropathy.	Malley et al (2001)	High
Renal	Chronic (>90 days)	Rat, Other Female (62)	0, 87.8, 283, 939 mg/kg-bw/day (0, 1600, 5000, 15,000 ppm)	2 years	Not Reported	NOAEL = 939 mg/kg - bw/day	No exposure-related adverse effects	Malley et al (2001)	High

Target Organ/ System	Study Type	Species, Strain, Sex (Number/ group)	Doses/ Concentrations	Duration	Author Reported Effect Dose or Conc. (NOAEL, LOAEL, LC_{50})	EPA Identified Effect Dose or Conc. (NOAEL, LOAEL, LC_{50})	Effect Measured	Reference	Data Quality Evaluation
Renal	Chronic (>90 days)	Mouse, B6C3F1 - Male (50)	0, 89, 173, 1089 mg/kg-bw/day (0, 600, 1200, 7200 ppm)	18 months	Not Reported	NOAEL = 1089 mg/kg - bw/day	No adverse effects	Malley et al (2001)	High
Renal	Chronic (>90 days)	Mouse, B6C3F1 - Female (50)	0, 115, 221, 1399 mg/kg-bw/day (0, 600, 1200, 7200 ppm)	18 months	Not Reported	NOAEL = 1399 mg/kg - bw/day	No adverse effects	Malley et al (2001)	High

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H.1.7 Hazard and Data Evaluation Summary for Cancer Studies

Table_Apx H-7. Summary of Tumor Incidence Data from Animal Cancer Bioassays

Species/ Strain/ Sex (Number/group)	Exposure Route	Doses/ Concentrations	Duration	Cancer Incidence	Effect	Reference	Data Quality Evaluation
Rat/Crj: CD(SD)/ Both (120)	Inhalation, whole body	0, 41, 405 mg/m^3	6 hours/day 5 days/week for 2 years	Data not presented	Increased pituitary adenocarcinomas at 41 but not 405 mg/m^3 and at 18 but not 24 months	DuPont (1982)[a]	Medium (1.8)
Rat/Other/ Female (62)	Oral, dietary	0, 87.8, 283, 939 mg/kg-bw/day (0, 1600, 5000, 15,000 ppm)	2 years	0, 2, 3, 3	At least one mammary neoplasm	Malley et al. (2001)[b]	High (1.2)
Mouse/ B6C3F1/ Male (50)		0, 89, 173, 1089 mg/kg-bw/day (0, 600, 1200, 7200 ppm)	18 months	5, 2, 4, 12 [c]	Increased incidence of hepatocellular adenoma		
				4, 1, 3, 13 [c]	Increased incidence of hepatocellular carcinoma		
Mouse/B6C3F1/ Female (50)		0, 115, 221, 1399 mg/kg-bw/day (0, 600, 1200, 7200 ppm)		2, 2, 1, 7 [c]	Increased hepatocellular adenoma and carcinoma		
				0, 0, 0, 3 [c]	Increased hepatocellular carcinoma		

[a] This is the unpublished study of the published study identified as Lee et al. (1987)

[b] Unpublished study of the results in rats is available as NMP Producers Group (1997)

[c] $P < 0.05$ by Cochran-Armitage trend test

Appendix I PBPK MODELING

The PBPK models of (Poet et al., 2010) for describing the toxicokinetics of NMP in rats and humans were revised for use in deriving an occupational exposure limit (OEL). These PBPK models were initially evaluated and revised by EPA in 2013 (U.S. EPA, 2013c). Further modifications and calibration were conducted by Dr. Torka Poet in 2014 (personal communication). In this update, additional data were considered to further calibrate and validate the model. Model calibration consists of using data to optimize parameters when those parameters are unknown or approximated, validation is used to show the fits of the model to other datasets. EPA then evaluated the version submitted by Dr. Poet in 2014 and made some additional corrections and modifications as described below.

These PBPK models simulate the pharmacokinetics of NMP and its metabolite 5H-NMP in rats and humans, described briefly below. The models consist of nine main compartments: lung, richly perfused tissues, slowly perfused tissues, skin, fat, mammary, placenta, fetus and liver for NMP with a submodel for 5H-NMP. The model can simulate NMP exposures via the oral, inhalation and dermal routes. Dermal absorption occurs for contact with NMP liquid and vapor. Distribution of NMP to tissues is assumed to be flow-limited. The model includes mathematical descriptions of the growth of fetal and maternal tissues during gestation based on a previous PBPK model of pregnancy (Gentry et al., 2002). Due to extensive differences between rat and human gestation periods, separate rat and human models were developed. NMP metabolism was assumed to occur in the liver. NMP was assumed to be eliminated in exhaled air and urine. 5H-NMP was assumed to be eliminated by further metabolism and in urine. The physiological parameter values used in the model were obtained from the literature (Gentry et al., 2002; Brown et al., 1997) and biochemical constants for absorption, metabolism and elimination were fit to the available toxicokinetic data (Payan et al., 2002; Akesson and Paulsson, 1997; NMP Producers Group, 1995a; Midgley et al., 1992; Wells and Digenis, 1988). Further description of the PBPK model are available in (Poet et al., 2010) (U.S. EPA, 2013c) and the modifications described below.

I.1 Rat Model

Several corrections were made to the model code (.csl file) and supporting scripts (.m) files as received from Dr. Torka Poet (personal communication). The first few of these are general and described here.

Blood Flows

Since the placenta is a separate compartment for the 5-HNMP model, its blood-flow and volume were subtracted from the sums used for the 'rest of body' for 5-HNMP. Also, the term for blood flow from the placenta was added to the mixed-venous blood mass balance for 5-HNMP.

To assure flow mass balance, instead of calculating cardiac output (QC) as an initial amount plus the change from initial for each compartment, it was just calculated as the sum over all the compartments:

Equation I-1 Cardiac Output

```
! QC = QCINIT + (QFAT - QFATI) + (QMAM - QMAMI) + QPLA+ (QUTR - QUTRI)
QC = QFAT+QLIV+QSLW+QRAP+QSKN+QMAM+QPLA+QUTR ! pms, 8-13-13
```

Parameter Consolidation

In the provided files, some physiological and chemical-specific parameter were set in separate scripts; *e.g.*, skin transport parameters in the dermal exposure scripts. This approach creates the potential for inconsistent parameters between different exposure simulations. Therefore, most parameters are now set in the ratparam.m script except those which are experimental control variables (e.g., air concentration, duration of exposure) and pregnancy-specific parameters set in preg_rat_params.m. The final set of parameters used and any inconsistencies with previous values in ratparam.m that may have differed are noted in that script.

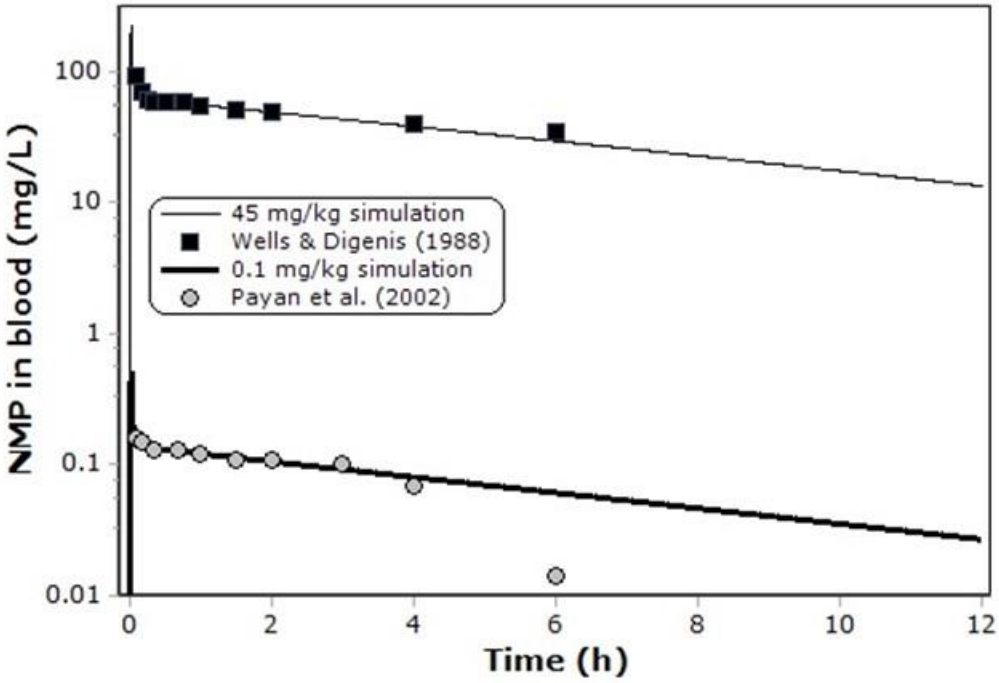
Recalibration (performed by T. Poet)

Additional data were used to calibrate and validate the intravenous, oral and dermal routes of exposure in rats. While plasma and urinary excretion data for major metabolite (5-HNMP) have also been reevaluated, primary attention has been paid to NMP, since the dose measure of interest are for the parent chemical. Model parameters for rats are set in the preg_rat_params.m and ratparam.m code scripts (preg_rat_params first calls ratparam), included in the acslX code package available with this assessment. Specific data and modeling choices for the rat are as follows.

Intravenous Data

All available intravenous data were obtained from studies that administered radiolabeled NMP. Most of the available studies only provided peak measured concentration and pharmacokinetic parameters. The study chosen to calibrate the model was that described by Payan et al. (2002), in which nulliparous rats were exposed to NMP doses ranging from 0.1 to 500 mg/kg. However, the authors only reported plasma NMP data for the lowest dose. This time-course data set was used to optimize metabolic rate parameters (VmaxC and Km) to describe the clearance of NMP from plasma. Unchanged NMP has only been found at very low levels in rat urine, so urinary elimination was set at a nominal value using a BW-scaled constant of KLNC= 0.0001 kg0.25/h. KLN = KLNC/(BW0.25) = 0.00014 h-1 for a 0.25-kg rat.

Payan et al. (2002) estimated the post-distribution metabolic rates of NMP from the disappearance of NMP from plasma in their studies. These estimated rates (Km=200 mg/L and VmaxC=1.5 mg/hr/kg0.75) were used as the seed values for the optimization carried out using the optimization routines supplied in acslX (v3.0.2.1; The AEgis Technologies Group, Inc, Huntsville, AL) in which the model was created. By starting with these values, it was hoped that the dose-range in that study would be represented and the optimized model would fit across doses. The final optimized parameters were Km= 225 mg/l and VmaxC=9 mg/hr/kg$^{0.75}$. Wells (1988) administered an intravenous dose of 45 mg/kg to rats, which is 450x higher than the dose used for optimization and this was used to validate the metabolic rates over a large range (Figure_Apx I-1).

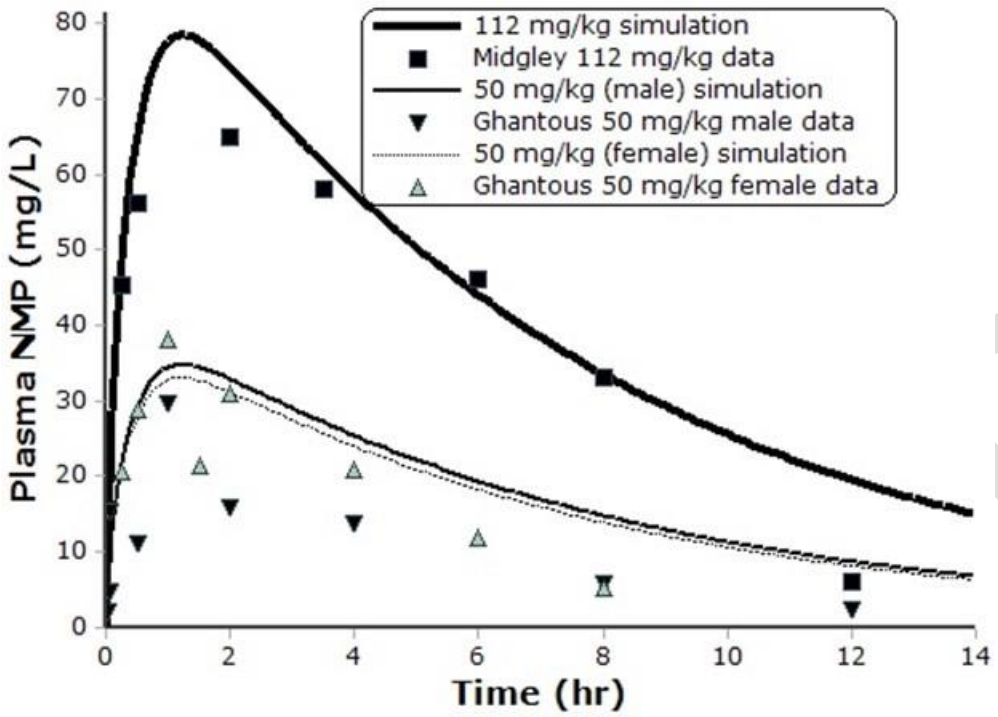


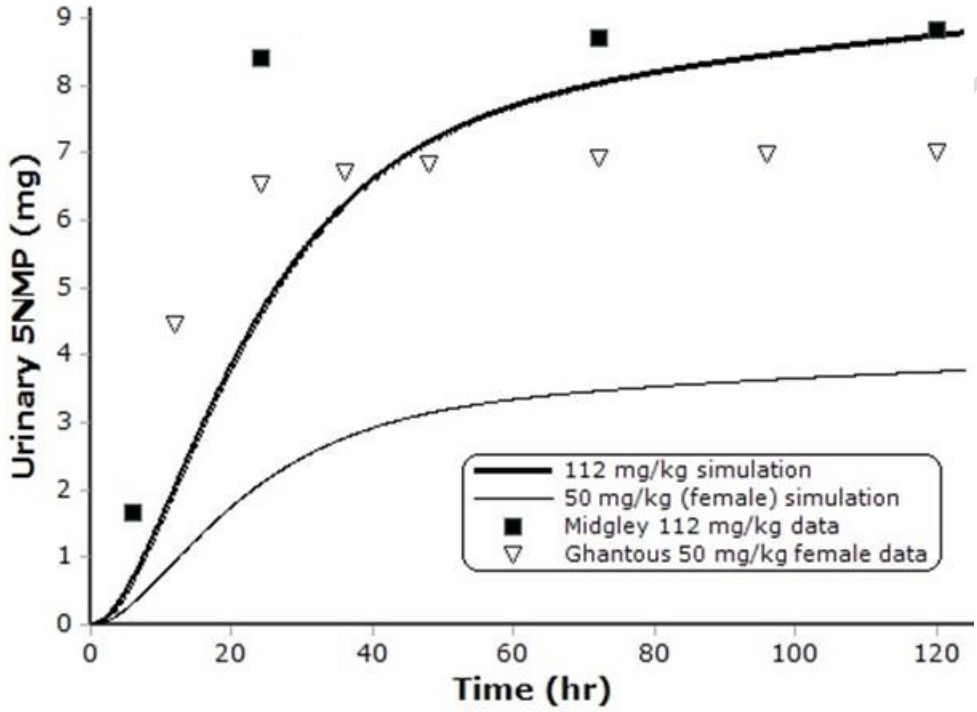
Figure_Apx I-1. Model Fits to IV Injection Data in Rats

Oral Data

All available oral exposure data were obtained from studies that administered radiolabeled NMP. The most valuable data sets are those that specifically measured NMP in blood (dose measure used in the assessment). NMP is highly metabolized and generally not found in urine as unchanged NMP. The study chosen to calibrate the oral absorption rate was described by Midgley et al. (1992). In this study, male and female rats received an oral gavage of 105 mg/kg (22.5 mg in rats weighing 192-239 g) NMP, co-exposed with 2-pyrrolidinone in a water vehicle. The authors concluded that 94.5% of the administered radiolabel was absorbed. However, when a constant (FRACOR) was fit to the data using the PBPK model the optimal value was found to be 93%.

The data indicate a rapid uptake and a slow elimination of NMP from plasma. Using the metabolic rate constants optimized to fit the intravenous dosing and the oral bioavailability measurements of Midgley et al. (1992), the model estimates of plasma NMP clearance resulted in a much higher AUC than the data indicated (Figure_Apx I-2). There is no suggestion of extra-hepatic (*i.e.*, intestinal) metabolism, so another mechanism to describe this absorption pattern was investigated. NMP is readily absorbed across membranes (see dermal absorption data discussion below) and for some chemicals absorption has been proposed to occur either in the stomach or quickly in the intestine, then more slowly during later phases of transport (Timchalk et al., 2002; Levitt et al., 1997; Staats et al., 1991). Therefore the original PBPK model was altered to include primary (stomach) and secondary (intestine) GI compartments to describe oral absorption following the description from Staats (1991). The resulting model predictions are vastly improved (Figure_Apx I-2). Using dual oral absorption results in ~75% of the absorbed dose (after multiplying by 93% bioavailability) being absorbed via the faster process and the remaining ~25% being more slowly absorbed. Also, an unusually high fraction of the radioactivity was found in the feed residue for the females in the NMP Producers Group (1995a) study, 4.5%, so the simulated dose for that group was decreased proportionately.





Figure_Apx I-2. Model Fits to Rat Oral PK Data

Dermal Model & Data

Corrections to the mass balance equations for the rat skin are as indicated in the commented code copied below. RASK is the rate of changes in the skin compartment. The equation for the amount in the compartment, ASK, includes the initial condition, ASK0, for the initial dermal application, but otherwise the correction to RASK makes it the standard format for PBPK models. As received the code had multiplied CSK rather than CSKV (skin venous blood concentration) by the blood flow (QSKN) for the rate of efflux in blood and had not separately calculated CSKV.

Equation I-2 Rat Skin Model Equations

```
RASK = QSKN*(CA - CSKV) + RADL ! NOW MINUS CSKV, NOT CSK; PMS 8-21-13
ASK = INTEG(RASK,ASKO) ! Initial value, ASKO, added for Becci et al. (1982)
! exposures; pms 8-14-13
CSK = ASK/VSK     !'NMP IN SKIN, MG/L'
CSKV = CSK/PSKB  ! NMP IN VENOUS BLOOD, PMS 8-22-13
```

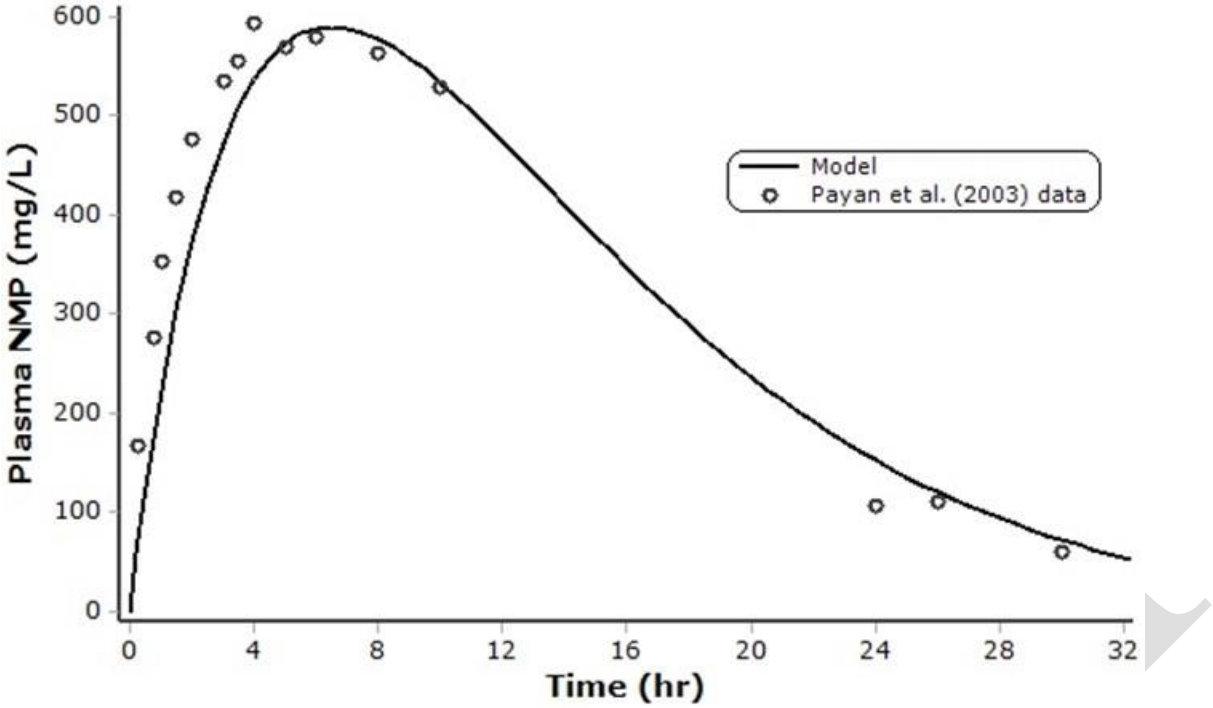
The corresponding flow term for transfer from the skin to the mixed venous blood compartment was also corrected (*i.e.*, to use CVSK instead of CSK).

While these changes to the skin compartment equations initially degraded the fits to the dermal exposure considerably, it also appeared that the associated partition coefficients were not consistent with the measured values reported by Poet et al. (2010), Table 5. They were recalculated as follows:

Equation I-3 Rat Skin Partition Coefficients

```
Skin:liquid, PSKL = 0.42: % value as measured for skin:saline, vs. 450
Skin:blood, PSKB = 0.12: % (skin:saline)/(blood:saline)
Skin:air, PSKA = 55:
% (skin:saline)*(blood:air)/(blood:saline) = (skin:blood)*(blood:air)
```

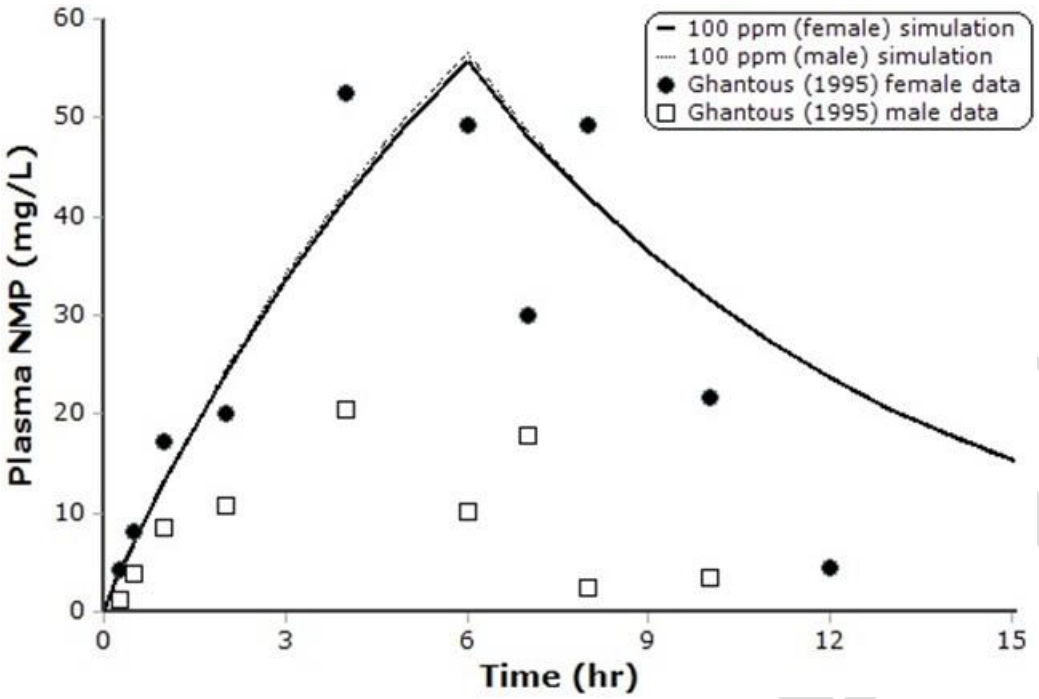
Developmental studies for NMP have been conducted by the dermal route (Becci et al., 1982). In the original PBPK model publication (Poet et al., 2010), the dermal route was assessed using a permeability coefficient (Kp) of 4.7×10^{-3} cm/hr that was approximated from *in vitro* studies (Payan et al., 2003). For the current assessment, the *in vivo* dermal exposure studies described by Payan (2003) were used to optimize Kp. In this study, rats were exposed to 200 µl of neat NMP. According to Payan et al., by 24 hrs after dosing, 80% of the NMP applied had penetrated the skin. The Kp value optimized to these data was estimated to be 4.6×10^{-3} cm/hr (Figure_Apx I-3), which is consistent with the range of Kp values estimated from the *in vitro* studies (from 2.0×10^{-3} to 7.7×10^{-3}cm/hr: (Payan et al., 2002)).



Figure_Apx I-3. Model Fits to Dermal PK Data from Payan et al. (2003) in Rats

Inhalation

No parameters were optimized to simulate the inhalation exposures of female rats to 104 ppm NMP for 6 hr (NMP Producers Group, 1995a), 100% inhalation bioavailability was assumed. These data, like the oral exposure data from the same source, appear to be more variable than from other studies. The model fits to the data are shown in Figure_Apx I-4.



Figure_Apx I-4. Model Simulations vs. Inhalation PK Data from Ghantous (1995a) for NMP Inhalation in Rats

Exposure Control for Bioassay Simulations

Because both Becci et al. (1982) and Saillenfait et al. (2002) explicitly stated that the animal BWs were measured every 3rd day of gestation and the dermal/oral doses were adjusted accordingly on those days (as BW increases during pregnancy), corresponding conditional (if/then) statements were added to the 'GAVD' and 'REAPPLY' discrete blocks, to re-calculate the doses on those days.

The code for the dermal discrete blocks follows. ASK0 is the total absolute amount applied; DSK is the dose/kg BW. Because Becci et al. (1982) rubbed the material into the skin, it is assumed to be added directly into the skin compartment (ASK), rather than as a liquid on top. Hence the dose is given as an addition of ASK0 (mg/day applied) to ASK.

Equation I-4 Dermal Dosing Equations

```
DISCRETE SKWASH          ! PMS, 8-14-13
        ASK = 0.0 ! Assume skin washing in Becci et al. (1982) removes all NMP IN skin
        if (DAYS.LT.15.0) SCHEDULE REAPPLY.AT.(T+DOSEINTERVAL-TWASH)
END

DISCRETE REAPPLY         ! PMS, 8-14-13
        IF (ROUND(DAYS).EQ.9.0) ASKO=DSK*BW
        IF (ROUND(DAYS).EQ.12.0)        ASKO=DSK*BW
        IF (ROUND(DAYS).EQ.15.0)        ASKO=DSK*BW
        ASK = ASK + ASKO
        SCHEDULE SKWASH.AT.(T+TWASH)
END
```

Also, because Becci et al. (1982) washed the skin area exposed to dermal application at the end of a set time interval, a "SKWASH" discrete block was introduced at which time the amount in that patch of skin was assumed to be momentarily reduced to zero. During periods of dermal application, transport from the liquid to the skin was turned on using the pulse function, DZONE. After removal of the liquid it was assumed that NMP in the skin patch could volatilize into the otherwise clean air, with the rate defined by the same permeability constants, but using the skin:air partition coefficient.

The rate of transfer to/from the skin area is then defined by:

Equation I-5 NMP Dermal Transport

```
RADL=(KPL*SA/1000.0)*((CSURF-(CSK/PSKL))*DZONE - (1.0-DZONE)*(CSK/PSKA))
! 2ND term, (1.0-DZONE)*(CSK/PSKA), allows for evaporative loss when DZONE=0
```

The primary part of this equation for transfer when liquid is in contact with the skin, (KPL*SA/1000.0)*(CSURF-(CSK/PSKL)), is identical to that used previously by McDougal (1986). Finally, a constant, CONCMGS, was introduced so that the air concentration could be set directly in mg/m^3. This is converted to the concentration in mg/L (CONCMG) in the code and added to the inhalation exposure, turned on and off using the switch, CIZONE, which is turned on and off using SCHEDULE/DISCRETE statements:

Equation I-6 NMP Vapor Exposure Control

```
CI = CCH*PULSE(0., DOSEINTERVAL,TCHNG) + CIZONE*CONCMG  ! MG/L
! Added CIZONE*CONCMG, PMS, 8-13-13
```

I.2 Human Model

Human exposures to NMP will be primarily via the inhalation route; contribution from the dermal route (vapors or liquid) may also be significant if not primary for some scenarios. Ingestion of NMP is not expected to be a significant pathway in human populations. Both controlled and occupational human exposure data are available from the published literature. Controlled human biomonitoring studies were used to calibrate NMP and 5-HNMP metabolic rates and a workplace exposure assessment study was used to validate the model and exposure scenarios.

I.2.1 Corrections to Human Model Structure

NMP Metabolism and Urinary Elimination

Since the human PK data were consistent with a nearly linear model (first-order kinetics, including metabolism) estimation of a metabolic saturation constant, Km, using the traditional Michaelis-Menten equation for metabolism of NMP, was difficult. In particular as estimates of Km became larger, model fits became less sensitive to variation in its value. Therefore, equation was changed from the standard form, rate = Vmax*C/(Km + C), where C is the concentration of NMP in the liver, to the equivalent form, rate = VK1*C/(1 + AF1*C), where VK = Vmax/Km and AF1 = 1/Km. These two forms are mathematically identical given the relationship between parameters just shown. The affinity constant, AF1, can be easily bounded to be non-negative and possibly converge to zero, corresponding to an indeterminately large Km. Since VK represents hepatic metabolism, it was assumed to scale with BW

the same as Vmax; *i.e.*, VK1 = VK1C*BW0.75. The urinary elimination of NMP was assumed to be first order, rather than saturable, using a rate constant (KUMNE) that was not scaled by BW.

5-HNMP

Since 5-HNMP is not being considered as an internal metric for toxicity and its volume-of-distribution (VOD) appeared to be over-estimated using the original PBPK model structure and measured tissue partition coefficients, its description was replaced with a classical one-compartment PK model. Further, as the metabolism of 5-HNMP also appeared to be linear and the data for estimating a Km value even weaker, a transformation of its metabolic rate equation like that for NMP described just above was assumed, but with the affinity assumed to be effectively zero, resulting in a first-order metabolic rate equation. As with NMP, the urinary elimination of 5-HNMP was also assumed to be first-order. The resulting model then becomes:

Equation I-7 5-HNMP Metabolism and Elimination

d A5H/dt = RAMET1*STOCH – RAMETM1 – RAUHP
(rate of change of amount of 5-HNMP)
CVEN1 = A5H/VOD5H (concentration of 5-HNMP in venous blood)
VOD5H = VOD5HC*BW (volume of distribution assumed to scale with BW)
RAMETM1 = ¬CVEN1 *VK2, where VK2 = VK2C*BW0.75
(rate of metabolism of 5-HNMP)
RAUHP = KME*CVEN1 (rate of urinary elimination of 5-HNMP)
RAMET1 = rate of NMP metabolism to 5-HNMP (mg NMP metabolized/h)
STOCH = ratio of 5-HNMP to NMP molecular weights.

Exposure and Timing Control

A table function, RESLVL, was added as a place-holder for reading in defined (consumer) inhalation exposure time-courses; specifically from EPA exposure assessment modeling.
A constant, GDstart, the day of gestation on which the simulation starts and a variable Gtime, the hrs into gestation, were added to facilitate separating exposure control from gestation timing.

A second set of DISCRETE/SCHEDULE blocks were added to allow for split exposure scenarios (morning/afternoon worker exposure; dual-episode consumer exposures). DZONE, set in the DISCRETE/SCHEDULE blocks, controls the time within a day when discontinuous exposure occurs. Czone is the product of DZONE and a pulse function used to control for days/week exposure in workplace scenarios:

Equation I-8 Vapor Exposure Scheduling

Czone = pulse(0.0,fullweek,hrsweek)*DZONE ! pms 8-20-13
! for a 5 day/wk exposure, use fullweek=7*24, hrsweek=5*24 (Dayswk=5)
! for a single day, fullweek=1e16, hrsweek=24 (Dayswk=1)

A binary constant, BRUSH, was added to set exposure scenarios when dermal contact with liquid occurs. For workplace scenarios, exposure to vapor and liquid are assumed to be simultaneous; *i.e.*, the worker leaves the location with NMP vapor and washes his/her hands when he/she has finished applying the material.

Skin Compartment

The original skin compartment which is coded to include uptake from liquid-dermal contact was renamed by adding "L" to the end, SK → SKL and a second skin compartment to account for concurrent vapor-skin uptake, SKV, was added. This was done because when the human model was calibrated for inhalation exposure, an exposed skin surface area of 6700 cm^2 was used. When this surface is reduced to ~ 0, predicted blood levels of NMP are reduced ~ 45%. Thus vapor uptake through the skin is a significant component of inhalation exposure and there is no reason to assume, a priori, that this uptake (or desorption) does not occur through a similar area of exposed skin during workplace and consumer exposures, except for any area that would have liquid contact or otherwise be occluded (*e.g.*, by protective equipment). So the SKV compartment allows for simultaneous absorption of vapor-through-skin that does not have liquid contact and from areas of skin with liquid contact. The surface area of SKV and SKL are SAV and SAL, respectively. SAL can set directly for different exposure scenarios.

To account for variations with individual BW, a parameter for the fraction of skin area exposed to vapor was introduced: SAVC, with SAV = SAVC*TSA, where TSA is the total body surface area. TSA is calculated for each individual based on BW and height. For EPA simulations, SAVC was set to 0.25, representing the head, neck, arms and hands, minus any area assumed to have liquid contact or covered with protective gloves or a face-mask.

The rate for delivery from a liquid film to the 'SKL' skin compartment (also see further below) is then defined by:

Equation I-9 NMP Liquid Rate of Delivery to Skin

```
RADL = (PVL*SAL/1000.0)*(CSURF-(CSKL/PSKL))*Czone*BRUSH
        ! Net rate of delivery to "L" skin from liquid, when liquid is there
```

The equations for transfer of vapor (air concentration = CI) to the SKL compartment, which occurs during periods with no liquid/spray contact for the SKL compartment are similarly:

Equation I-10 NMP Vapor Rate of Delivery to Skin

```
RADVL = (PV*SAL/1000.0)*(CI - (CSKL/PSKA))*(1.0-Czone*BRUSH)
! Net rate of delivery to "L" skin from air, when liquid not present
```

Since the dermal exposures are to neat or highly concentrated preparations of NMP, it would not be appropriate to assume that the residual liquid volume on the skin remains constant as absorption occurs. Further assuming that water penetration of the skin is minimal, the amount of water in the liquid solution is assumed to remain constant. The initial volume on the skin is defined by a new constant VLIQ0 and the density of NMP at 40C (~ skin temperature) = DENSITY = 1.02×10^6 mg/L. To avoid potential divide-by-zero errors, the nominal initial concentration (CONCL) is reduced by 1 mg/L (1 ppm) when computing the initial amount of NMP and water in the liquid:

Equation I-11 NMP Unabsorbed Fraction Remaining on Skin

```
DDN = (CONCL - 1.0)*VLIQ0*FAD
! Subtract 1 mg/L, ~ 1 ppm, from initial conc. to avoid VLIQ --> 0
AH20 = (DENSITY+1.0-CONCL)*VLIQ0 ! ... and add it to H20. pms 9-16-14
```

A mass-balance equation was then added to attract the remaining amount and volume on the skin surface, which is then used to calculate the concentration:

```
ASURF = INTEG(-RADL, DDN) ! Amount in liquid. DDN is the initial amount.
```

VLIQ = (AH20 + ASURF)/DENSITY
CSURF = ASURF/VLIQ

This volume balance is important for analysis and calibration of the dermal PK studies where small volumes (5 or 10 ml) were applied at the beginning of the exposure and not replenished. However in workplace and consumer user exposures, it is assumed that fresh liquid is constantly replacing any NMP that is absorbed, keeping the surface concentration essentially constant. Therefore the initial volume, VLQ0, is set to a large value (10^6 L) for those scenarios.

The skin partition coefficients were also recalculated as was done for the rat, with rat parameters for skin:saline and blood:air, but human blood:saline.

Tissue and Blood-Flow Mass Balances

The model had been previously coded with an alveolar blood compartment (ALV), but this was commented out in the DYNAMIC section. Therefore this volume fraction should not be subtracted when calculating the slowly-perfused volume. The fraction of blood-flow to slowly perfused tissue was updated to also account for the SKV compartment; on the other hand a separate skin compartment is not used for 5-HNMP, so the skin blood flow is NOT subtracted for the metabolite-slowly-perfused compartment (SLW5). These have all been corrected.

QSKCC (original fractional flow to the skin) had been subtracted twice, both in calculating QSLWC and then in the calculation of QSLW. The 2nd subtraction created a mass balance error and hence was removed. On the other hand, placental blood flow is now subtracted, so the total flow to slowly-perfused continues to total cardiac output minus all other tissue/group flows.

For tissues for which the volume changes with gestation day, the initial values were corrected to match the calculation in the DYNAMIC section, which apply at the first time-step. In the dynamic section, the calculation of QC was corrected to include the *increase* in placental flow (QPLA – QPLAI) rather than the total placental flow (QPLA), since QCINIT includes QPLAI. QSLW5 and VSLW5 (5-HNMP slow compartment flow and volume) are now calculated in the DYNAMIC section by subtraction. The calculation of QC was otherwise left in its original form, in contrast to the rat PBPK model.

Parameter Consolidation

Like the rat model, the human model physiological and biochemical parameters are now primarily set in a single script, human_params.m. Initial values for the metabolic and vapor-absorption (KPV) parameters were obtained by fitting Bader et al. (2006) inhalation data with the exception of the high-concentration data from one individual, but the data otherwise grouped without distinction between individuals (further details below). An alternate set of fitted parameters was obtained by fitting the data for each individual separately, focused on the low-concentration data and then calculating the average of each parameter across the individually-fitted values. This subset of parameters is selected by using human_avg_params.m. Since further analysis of the dermal absorption of liquid NMP showed that this uptake differed between neat (100%) NMP and diluted (50%) NMP, separate value of PVL were obtained for neat vs. diluted NMP (also see below). Hence only constants which define specific exposure scenarios (include skin areas exposed) and PVL are defined in the specific simulation scripts.

Inhalation Data

A study conducted by the Hannover Medical School, University of Dortmund, Germany (Bader and Van Thriel, 2006) was used to calibrate inhalation parameters of the model. In this study, 8 healthy, non-smoking, male volunteers were exposed to 10, 40 or 80 mg/m^3 NMP in an environmental chamber. Over the course of several weeks, each volunteer was exposed sequentially to all 3 concentrations. The 8 volunteers were separated into 2 groups of 4 and each group was exposed in a shared chamber. The exposures were carried out in ascending concentrations, with a 1-week period between each session. Volunteers wore slacks and T shirts and thus had arms exposed to vapor. Blood was collected from each volunteer in the middle of the 6-hr exposure period, at the end of exposure (6 hr) and 1, 2, 3, 18 and 42 hrs after the end of exposure. Urine was also collected from each volunteer at times up to 42 hrs after the end of exposure. Because it is relatively rare to have blood and urine data for multiple exposure levels, multiple time points, in individuals, efforts were made to ensure the exposure scenarios for these data were modeled as accurately as possible.

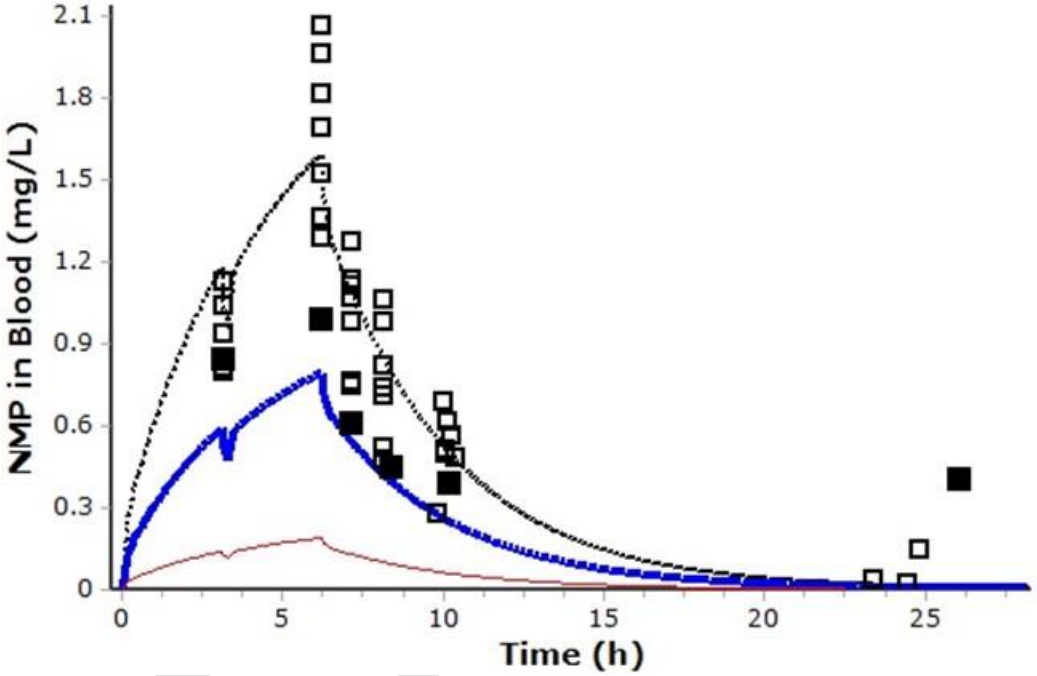
To collect the mid-exposure blood samples, volunteers left the chamber one at a time and moved to another room to have blood drawn and to give a urine sample. The data are consistent with a sharp drop in concentration for the mid-exposure blood sampling, when the peak NMP concentration measured at the end of the exposures are considered. In the report, the time taken to leave the chamber, walk to the new room, donate blood and urine was suggested to be about 10 minutes. However, exact times were not recorded. The notes indicate that the time between blood collection and urine collection was at least 5 minutes. In addition, the recorded times for collection of blood from first collected sample to last (*i.e.*, between the first and fourth volunteers to leave the chamber) was up to 55 minutes. If the times were equivalent for each subject and the volunteers only left the chamber as the previous volunteer returned, this would indicate an average of 12 minutes was needed for sample collection from each volunteer.

Based on a careful review of the data tables in Bader and van Thriel (2006) and personal communication with Dr. Michael Bader and Dr. Christoph van Thriel, it was determined that each subject entered and left the exposure chamber at different times as described just above and were likely not sampled at exactly the same time after the beginning and end of each exposure segment. While the total exposure time for each subject was monitored and kept to exactly 6 h on each exposure day, based on the timing of the blood and urine samples (taken outside the exposure chamber), it is clear that the study design was not exactly followed. In particular, while the morning and afternoon exposures were supposed to be 3 h each, the time between the mid-day and first afternoon blood samples was less than 3 h for some individuals in some exposures (and the mid-day sample was taken much later after noon for such samples). In these cases it seemed likely that the individual spent slightly more than 3 h in the chamber in the morning and slightly less in the afternoon, for that exposure. Based on the recorded data and communications, the exposure timing used for modeling and simulation was set to 3.1 h for the morning exposure, a mid-day break of 0.2 h (12 min) and 2.9 h for the afternoon exposure. Since individual subjects did not enter and exited the chamber at exactly the same time, the time of their entrance to the chamber for each exposure was estimated based on the recorded times of the blood and urine samples. The sample times used for modeling were then calculated relative to the estimated entry times.

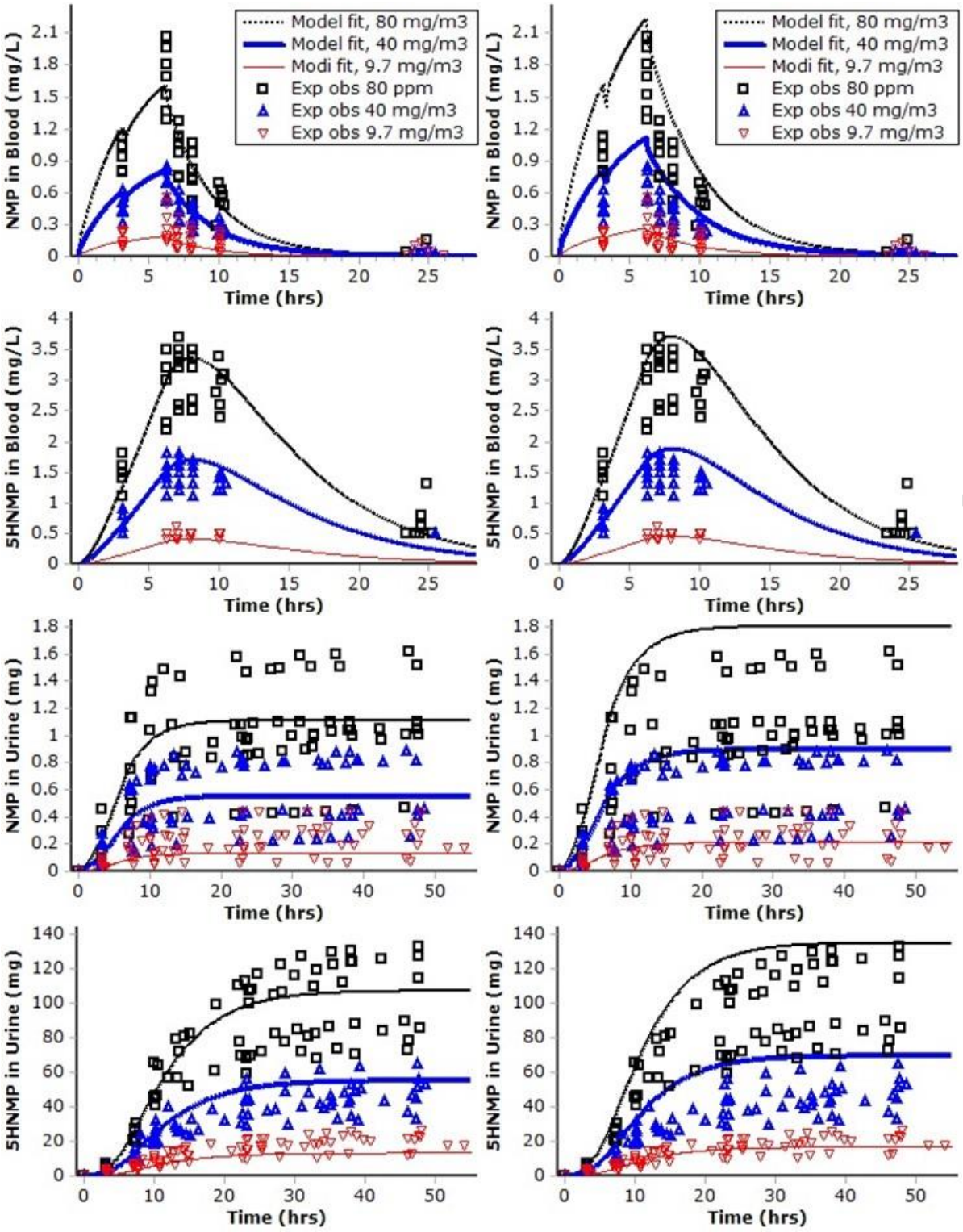
It was also clear that a number of the measurements, especially those of 5-HNMP for the low-concentration exposure, were recorded as the limit-of-detection (LOD), when the measured value fell below this limit. This was confirmed with Dr. Bader (personal communication). Therefore all measurements at/below the LOD were removed from the data set to avoid the bias they would otherwise introduce.

It also appeared that the high-concentration-exposure (80 mg/m^3) for one subject deviated substantially from the other subjects; see Figure_Apx I-5 below. Since the blood concentration at 6 h was well below those of the other subjects and that at 24 h well above (4 subjects had levels below the LOD), this individual's high concentration set was excluded from analysis of the grouped data. Blood concentrations at the middle and low exposure for this individual were among the range of the other subjects, hence included in the group data.

With this one data set removed, the revised model was fit to the group data for exposures at 9.7 and 80 mg/m^3, by adjusting the following parameters: PV, VK1C, AF1, KUMNE, VK2C, VOD5HC and KME. Since the data for the 40 mg/m^3 exposure were consistent with the 80 mg/m^3, but the data for 9.7 mg/m^3 appeared not to be and it was considered especially important to describe low-concentration exposures, the 40 mg/m^3 data were excluded from this exercise. The resulting parameter values are as follows, with model fits to the group data shown in Figure_Apx I-6, left side. These fits are compared to ones obtained by fitting the data for each individual separately, where possible using only the low-concentration exposure data and then calculating the average across the individual fits for each parameter (right side of Figure_Apx I-6; details below).



Figure_Apx I-5. NMP Blood Concentration Data from Bader and van Thriel (2006)
Curves are simulations for 9.7, 40 and 80 mg/m^3 exposures. Squares are individual blood concentration data for the 80 mg/m^3 exposure. Solid squares are from the one individual with the highest BW and height (102 kg, 190 cm), compared to the other subjects (65-80 kg, 168-183 cm).



Figure_Apx I-6. Alternate Fits to Collective Data from Bader and van Thriel (2006)
Left panels show fits to the groped data for 9.7 and 80 mg/m^3 (data shown). Simulations in right panel used average of parameters fit to each individual separately, primarily for 9.7 mg/m^3 (see text for details).

Parameters fitted to group data for 9.7 and 80 mg/m^3 exposures	**Average of parameters fit to data for each individual separately, primarily 9.7 mg/m^3**
PV = 1.6 (cm/h)	PV = 16.4 (cm/h)
VK1C = 0.47 (L/(h*kg$^{0.75}$))	VK1C = 0.386 (L/(h*kg$^{0.75}$))
AF1 = 0.02 (L/mg)	AF1 = 0.02 (L/mg) [fixed at group-fit value]
VK2C = 0.035 (L/(h*kg$^{0.75}$))	VK2C = 0.0359 (L/(h*kg$^{0.75}$))
VOD5HC = 0.26 (L/kg)	VOD5HC = 0.243 (L/kg)
KME = 2.3 (L/h)	KME = 2.75 (L/h)
KUMNE = 0.092 (L/h)	KUMNE = 0.103 (L/h)

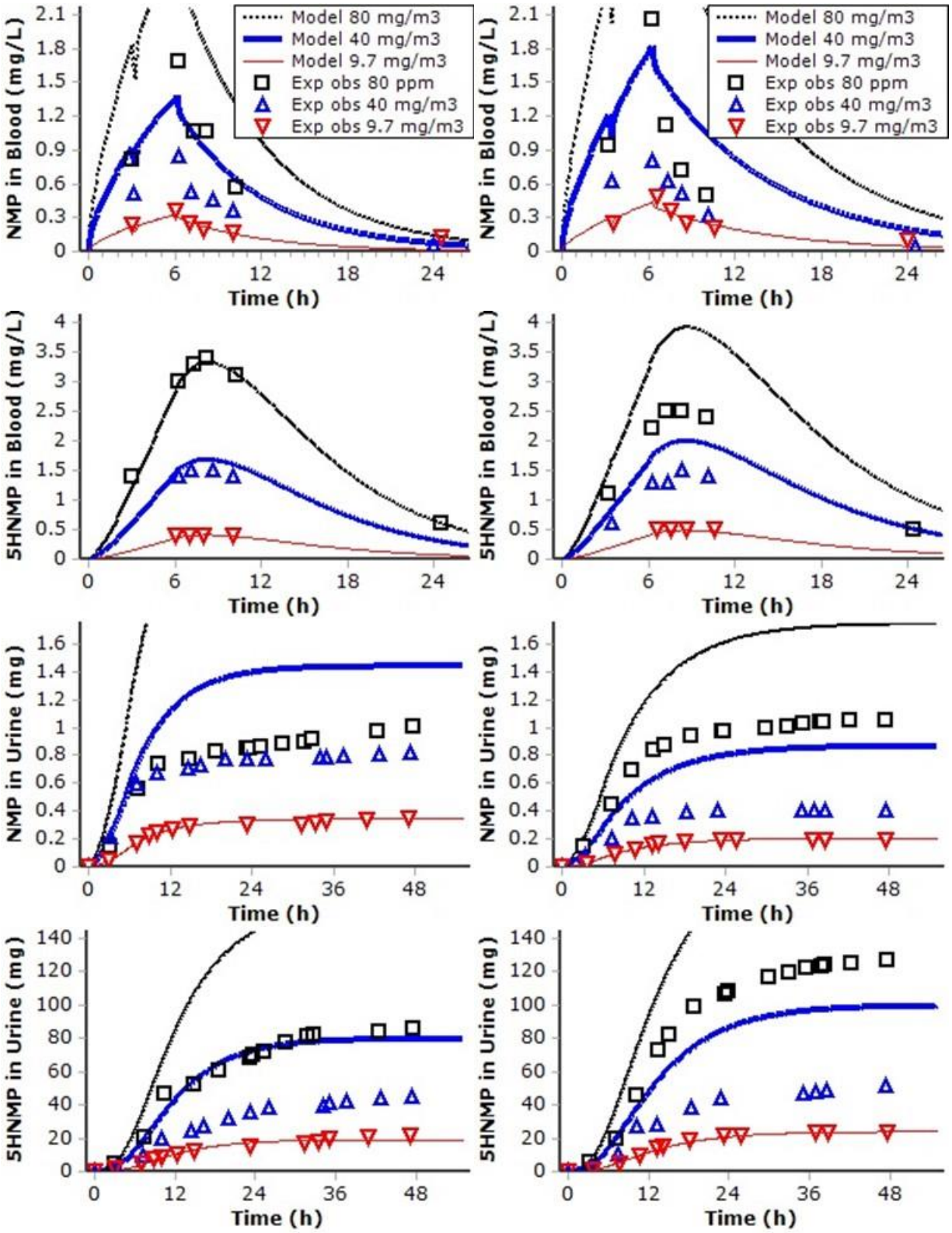
In their summary statistics, Bader and van Thriel (2006) reported group-averages of the peak NMP blood levels as being 0.293 mg/L for the 9.7 mg/m^3 and 1.585 mg/m^3. The ratio of these two (1.585/0.293 = 5.4), is considerably less than one would expect assuming linearity with exposure level (80/9.7 = 8.25) and is the opposite of what one would expect due to metabolic saturation of the conversion of NMP to 5-HNMP. This is not true for the ratio peak 5-HNMP levels in blood (8.08), however, which is comparable to the relative exposure level. If the nonlinearity in NMP blood levels were due to more efficient metabolism at the higher exposure level, then ratio of 5-HNMP blood levels would have been greater than expected.

Since the mechanism for the nonlinearity in blood NMP levels is unclear and it would be undesirable to under-estimate NMP blood levels and hence human risks at lower exposure levels, it was decided to estimate parameters using only the low-exposure data, if possible or with minimal use of the high-exposure data. (For two of the subjects the blood levels of 5-HNMP did not rise above the LOD for the low exposure, making it impossible to estimate VOD5HC for them. Hence the 80 mg/m^3 blood 5-HNMP data were also needed to estimate their parameters.) Given the observation that the high-exposure data for one subject was disparate from the other subjects, it also seemed possible that the apparent nonlinearity in the average PK data was due to the mixing of data from the 8 subjects in the study. Therefore fits focused on the low-exposure data were conducted separately for each subject. Since limiting to the low-exposure data would provide almost no information on metabolic saturation and the affinity (AF1) obtained from the fits to the group data was quite low (0.02 L/mg), AF1 was held at that group-fit value for this exercise. The resulting parameter values are listed in Table_Apx I-1 and fits to the individual data shown in Figure_Apx I-7 - Figure_Apx I-10. In order to allow one to see the fit to the low concentration and otherwise compare the fits across individuals, the y-axis scale was held constant for each analyte across the individuals, though this meant that the simulation curves for the higher exposure data sometimes went off the top of the plot.

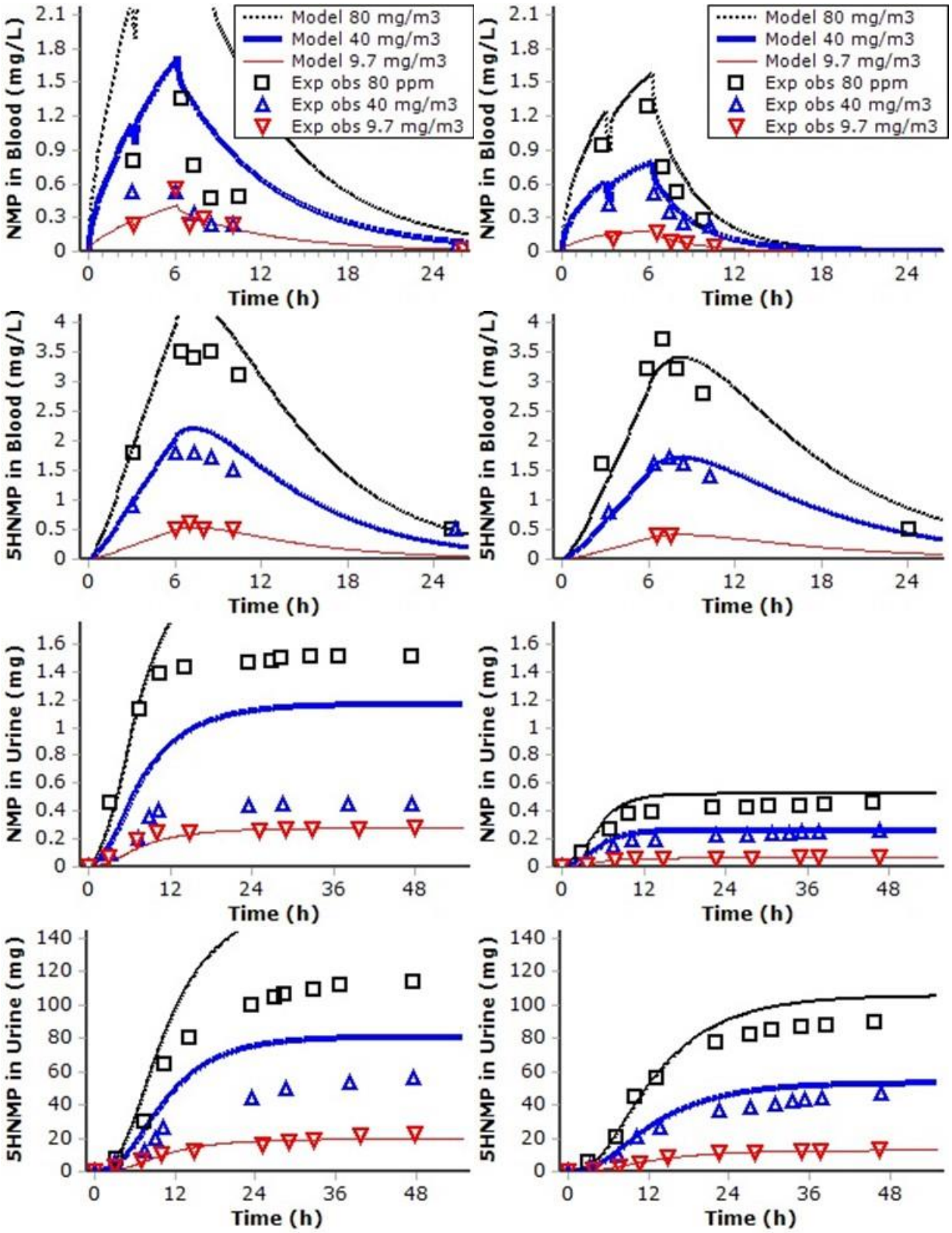
Table_Apx I-1. Estimated PBPK Parameters for Each Subject of the Bader and van Thriel (2006) Experiments

Subject	VK1C	KUMNE	PV	VK2C	KME	VOD5HC
1	0.25	0.11	19	0.017	3.2	0.2
4	0.17	0.042	34	0.004	3	0.14
10	0.22	0.069	35	0.027	2.8	0.12
12	0.63	0.046	12	0.044	1.9	0.39
14	0.57	0.2	10	0.08	2.5	0.4
16	0.45	0.06	0	0.08	1.9	0.2
17	0.38	0.2	20	0.02	4.3	0.26
25	0.42	0.1	1.5	0.015	2.4	0.23
average	**0.386**	**0.103**	**16.4**	**0.0359**	**2.75**	**0.243**

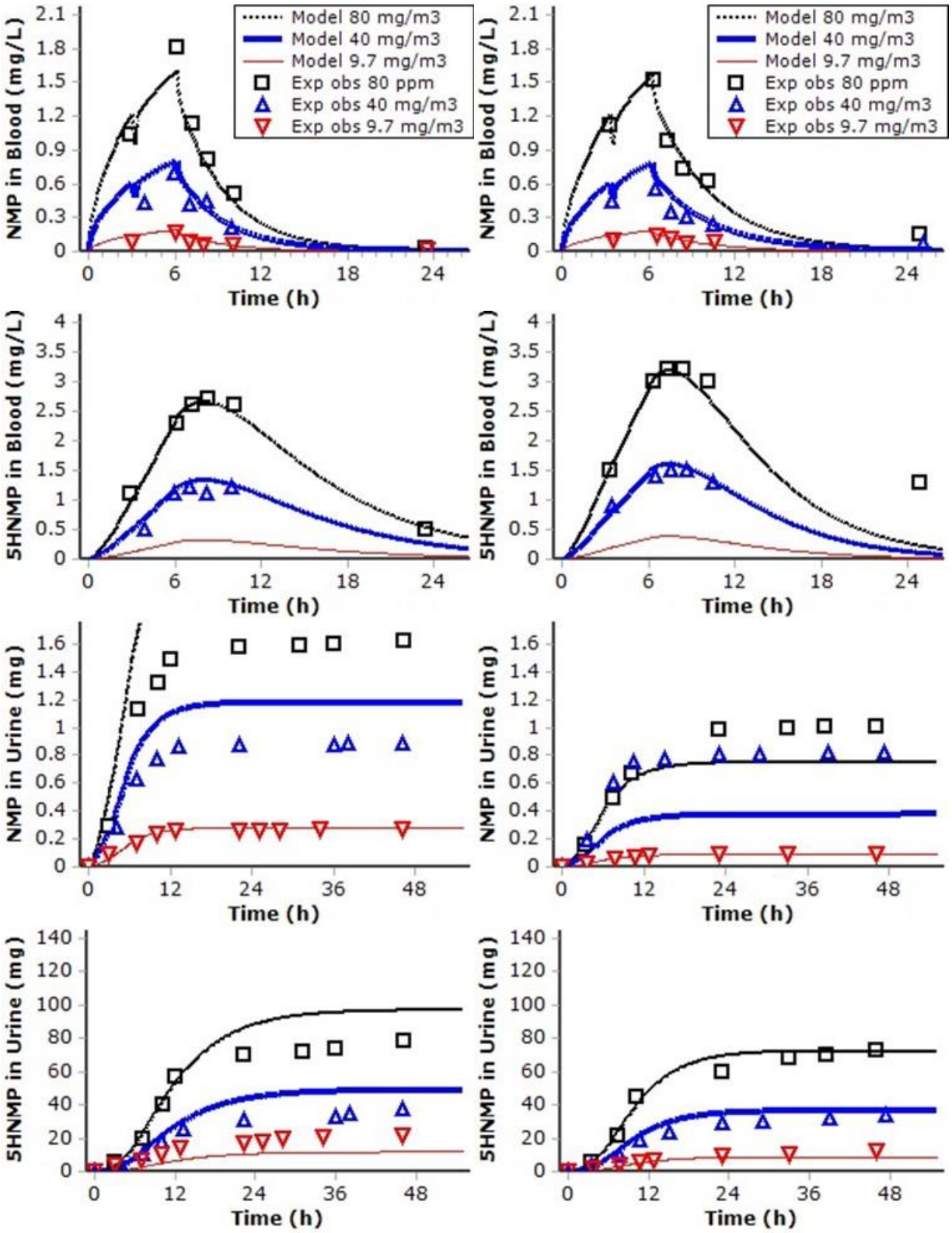
It is interesting to note that for half of the subjects (#12, #14, #16 and #25), the fits and data for NMP in blood show that the data are quite consistent with the essentially linear PBPK model, while for the other half the simulations with parameters fitted to the low-concentration data over-predict the high-concentration NMP data.



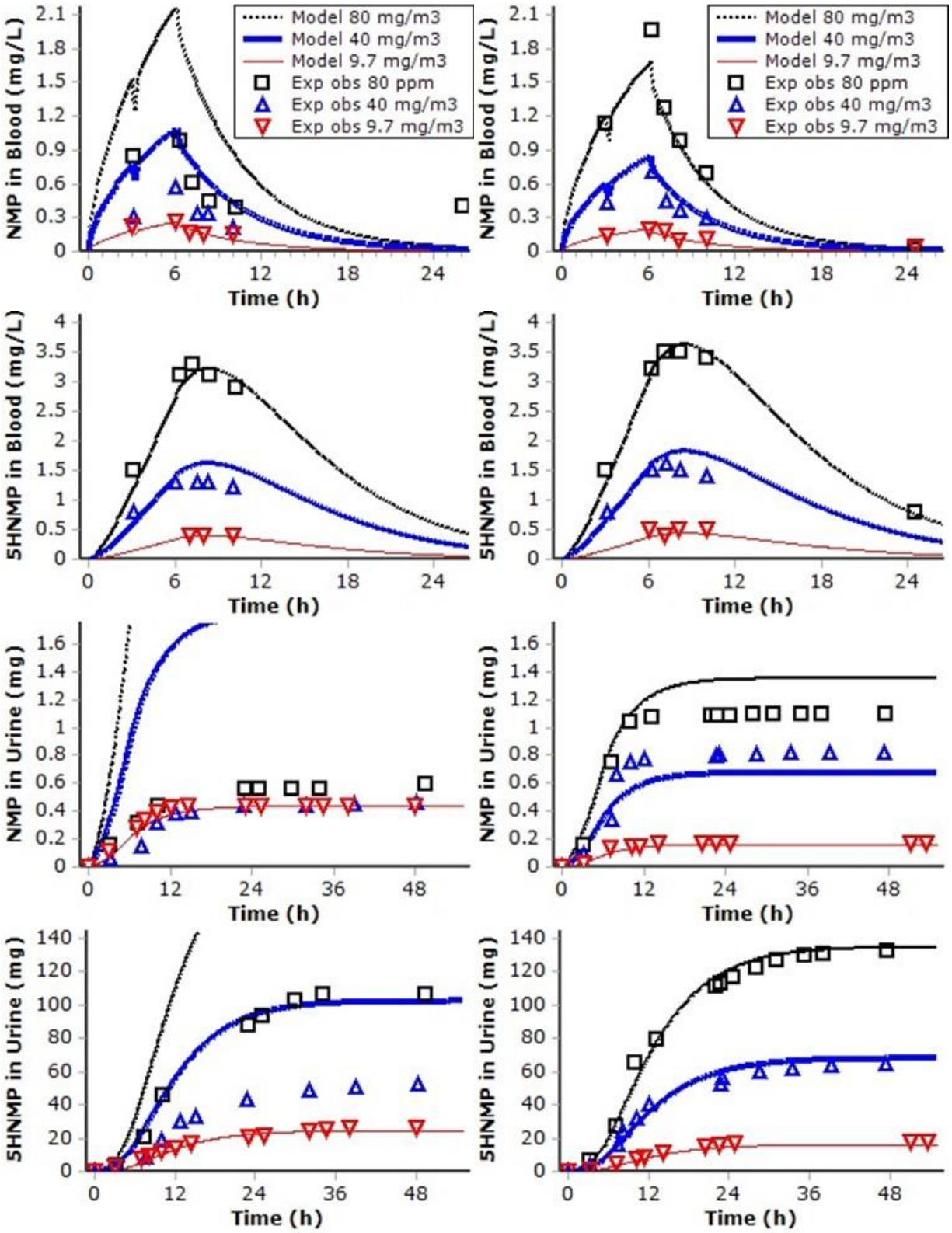
Figure_Apx I-7. Model Fits to Subjects 1 and 4 of Bader and van Thriel (2006)
Model fit separately to each subject. See text for details.



Figure_Apx I-8. Model Fits to Subjects 10 and 12 of Bader and van Thriel (2006)
Model fit separately to each subject. See text for details.



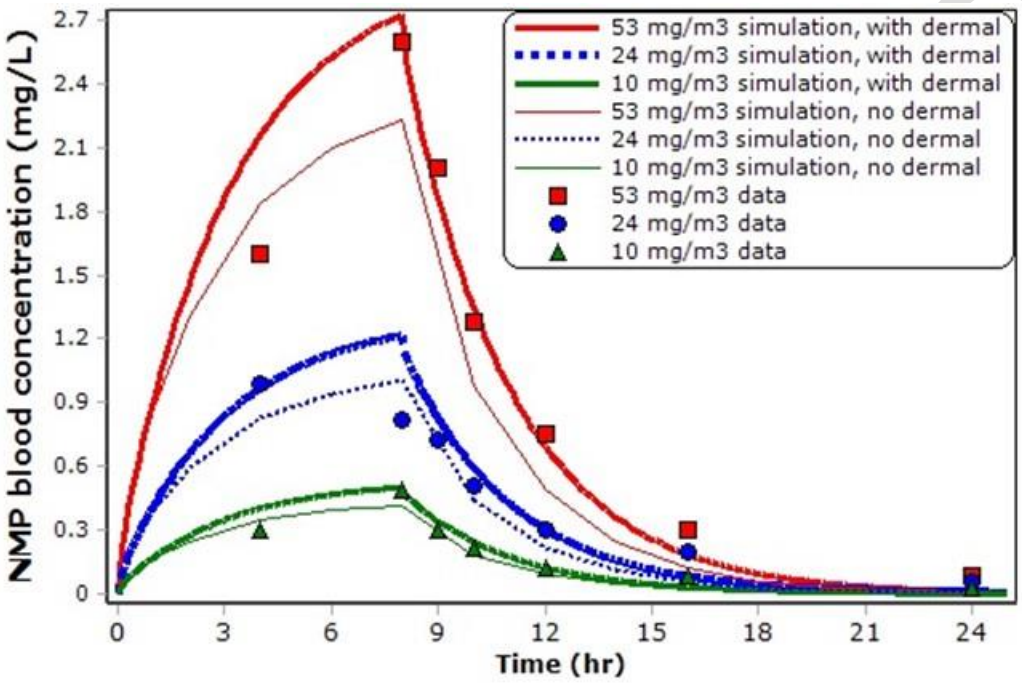
Figure_Apx I-9. Model Fits to Subjects 14 and 16 of Bader and van Thriel (2006)
Model fit separately to each subject. See text for details.



Figure_Apx I-10. Model Fits to Subjects 17 and 25 of Bader and van Thriel (2006)
Model fit separately to each subject. See text for details.

Dermal Data: Vapor and Liquid

Volunteers in the study described by Akesson and Paulsson (1997) wore shorts and t-shirts and thus also had dermal (vapor) exposures, as well as inhalation exposures, to NMP. The exposure concentrations for this study were similar to those of Bader et al (2005). With only inhalation exposures, the model under-predicted plasma NMP by about 25%, a vapor permeability coefficient, which accounts for both the skin permeability and the vapor/skin surface interaction, (PV) of 1.5 cm/hr was optimized to fit these data and is equivalent to the previously optimized value (Poet et al., 2010) (Figure_Apx I-11).



Figure_Apx I-11. Model Fits to Human Inhalation Data of Akesson and Paulsson (1997), With and Without Dermal Absorption of Vapors

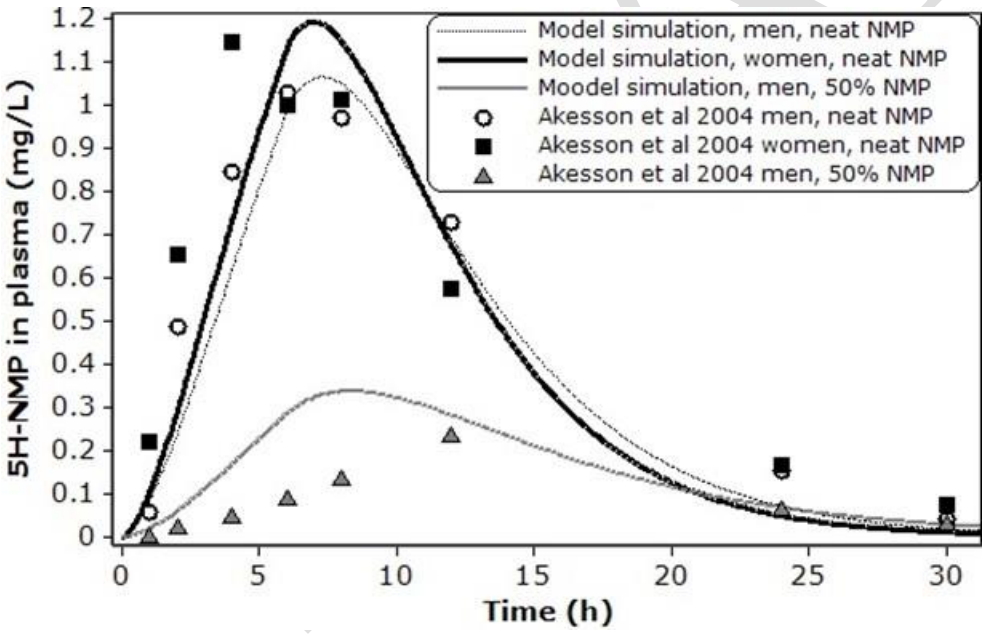
Model parameters were as obtained previously using the data of Bader and van Thriel (2006). Simulations are shown with dermal absorption of vapors included ("with dermal"; 25% of total surface area assumed exposed) or turned off ("no dermal").

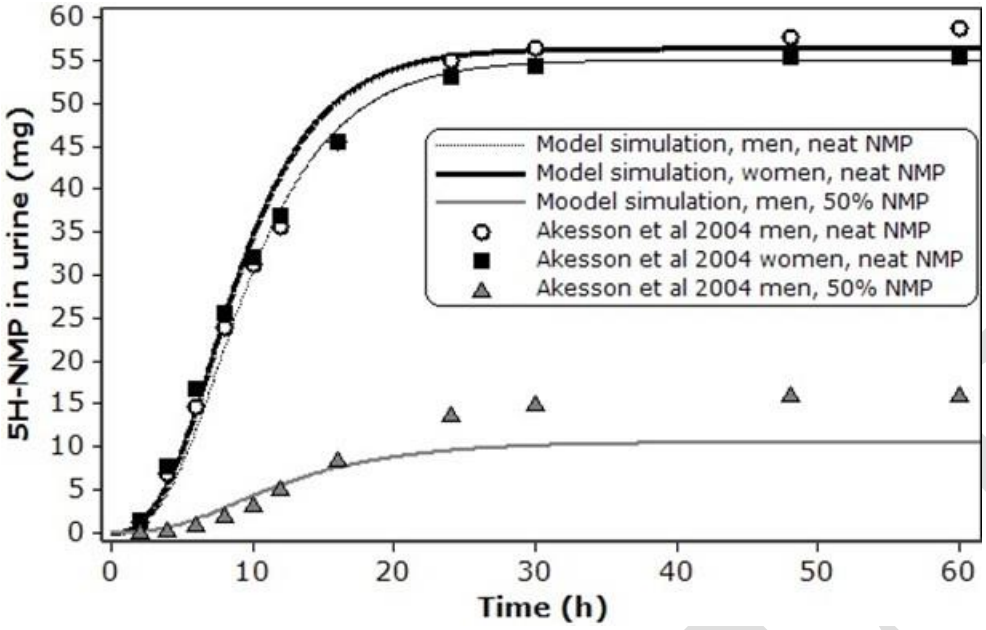
Akesson et al. (2004) exposed 12 volunteers (6 male and 6 female) to 300 mg NMP either neat or diluted 50:50 in an aqueous solution. Blood and urine 5-HNMP concentrations were monitored for up to 9 days. The plasma 5-HNMP concentration was extracted from the figure using DigitizIt (Braunschweig, Germany). Urinary 5-HNMP concentrations were extrapolated to total amount eliminated using the assumption that the average urinary flow for an adult is 18 ml/kg-day (Heffernan et al., 2014). Aqueous dilution resulted in a slower time to reach peak plasma 5-HNMP and a reduction in peak plasma concentration. Because the urinary elimination constant (KME) for 5-HNMP was seen to vary among subjects when fitting the Bader and van Thriel (2006) data (see Table H1) and we did not want a lack-of-fit to the urinary elimination data (which establish the mass balance, hence total amount absorbed) to adversely impact the fitting of the 5-HNMP blood levels, KME was also fit to each data set then. Optimized liquid Kp for neat NMP was 2.05 x 10^{-3} cm/hr (with KME = 4.54L/hr). To fit the data from the diluted exposures, a lower Kp of 2.87x10^{-4} was needed (with KME = 2.10 L/hr) (Figure_Apx I-12). These liquid dermal permeability coefficients were used in estimating human dermal absorption

for neat and diluted NMP absorption, though with KME kept at the average value from the Bader and van Thriel (2006) study (2.3 L/hr). (Note that KME does not impact NMP blood levels.)

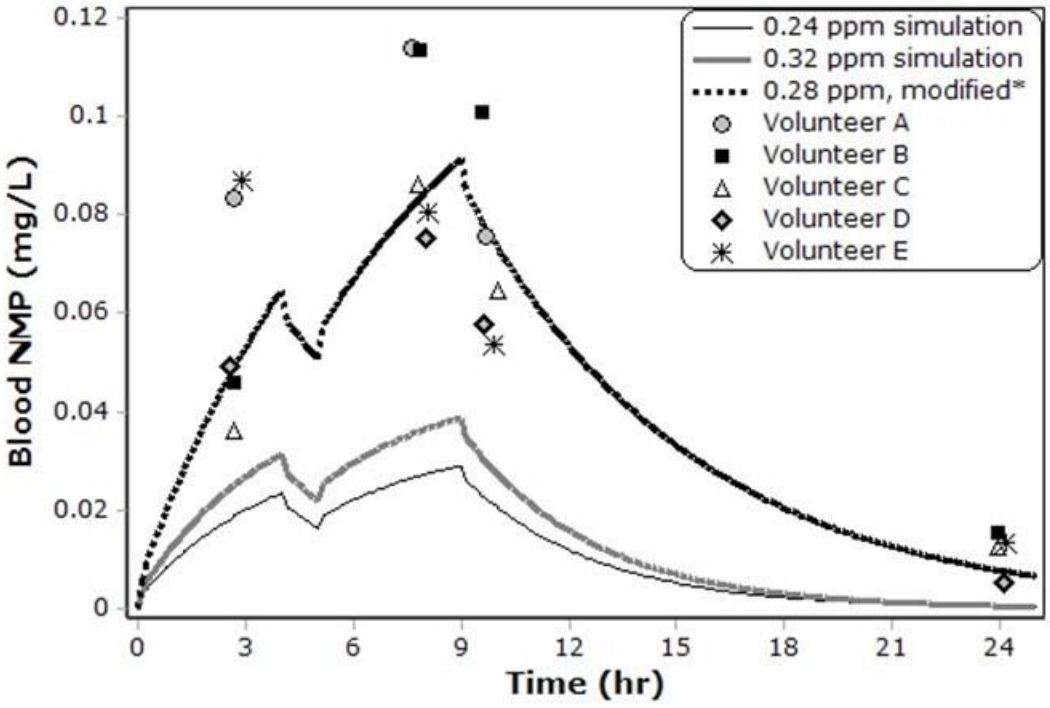
Workplace Observer Study

In a biomonitoring study Xiaofei (2000) followed 4 workers and 5 observers in a lens manufacturing facility. The workers washed lenses with NMP, working 11-hr shifts with a 1-hr lunch break (total 12 hrs within the facility). Observers were stated to be in the facility from 8 am to 5 pm for a single day, but the tabulated exposure metrics indicated only 8 h of exposure, so it was assumed that they also took a 1-hr break (at noon). The mean exposures for the observers was 0.28 ppm, with a range from 0.24 to 0.32 ppm. The PBPK model underestimated plasma NMP concentrations for the workers (data not shown) and observer by ~3x when no dermal exposure is assumed (Figure_Apx I-13). However, droplets of NMP were noted on the lenses as the workers were moving those lenses to drying racks. Just assuming that these droplets were due to some aerosolized NMP and that the observers had a small surface area of skin exposed to such droplets, 0.2 cm^2, gave results that better fitted the blood data during the exposure, but the clearance after exposure appeared to be too rapid. Assuming that the average metabolic rate was ½ of that identified from the Bader and van Thriel (2006) data (*i.e.*, VK1C = 0.193 L/h-kg0.75) with an even smaller exposure to aerosol (0.1 cm^2 of exposed skin) resulted in simulations that matched the data well (Figure_Apx I-13). The lowest individual VK1C estimated for the Bader and van Thriel (2006) data was 0.17 L/h-kg0.75, so the value used here is not unreasonable. In summary, the un-adjusted model gave simulations that were within a factor of three of this data set and the discrepancy can be explained by a reasonable level of metabolic variability between the two study populations and a small amount of dermal contact.





Figure_Apx I-12. Model Fits to Human Dermal Exposure Data of Akesson et al. (2004)



Figure_Apx I-13. Workplace Observer Simulations Representing Subjects of Xioafei et al. (2000)

*Metabolic elimination was reduced to ½ that estimated from Bader and van Thriel (2006) data and 0.1 cm^2 of skin was assumed exposed to liquid aerosol.