Summary of External Peer Review and Public Comments and Disposition

This document summarizes the public and external peer review comments that the EPA's Office of Pollution Prevention and Toxics (OPPT) received for the draft work plan risk assessment for n-Methylpyrrolidone (NMP). It also provides EPA/OPPT's response to the comments received from the public and the peer review panel.

EPA/OPPT appreciates the valuable input provided by the public and peer review panel. The input resulted in numerous revisions to the risk assessment.

Peer review charge questions[1] are used to categorize the peer review and public comments into specific issues related to the five main themes.

- General Issues on the Risk Assessment Document
- Worker Exposure Assessment
- Consumer Exposure Assessment
- Hazard and Dose-Response Assessment
- Use of PBPK Model
- Risk Characterization

[1] These are the questions that EPA/OPPT submitted to the panel to guide the peer review process.

General Issues on the Risk Assessment Document		
Charge Question 1-1: Please comment on whether the risk assessment provides a clear and logical summary of EPA's analysis. Please provide specific suggestions for improving the clarity and transparency of the risk assessment document. **Charge Question 1-2:** Please comment on whether appropriate background information is provided and accurately characterized. Please provide any other relevant literature, reports, or data that would be useful to support the risk assessment.		
#	**Summary of Peer Review and Public Comments for Specific Issues Related to Charge Questions 1-1 and 1-2**	**EPA/OPPT Response**
1	Several public and peer review commenters stated that the document is not clear about the overall objectives of the risk assessment.	EPA/OPPT has added language to clarify the objectives of the risk assessment. Specifically see the Executive Summary and Introduction (section 1.1)
2	A public commenter requested that the exposure estimates be clarified and refined, specifically the information contained in Table 3-7 and Table D-4.	EPA/OPPT has updated the description of exposure assessment methodology. All tables have been updated and exposure estimates have been refined. Please see Tables 2-1 through 2-5 and Appendices D & E.
3	Peer reviewers and several public commenters advocated the use of a PBPK model in the risk assessment.	The final risk assessment integrates a revised PBPK model. Section 1.2.4, Analysis Plan, describes how the PBPK model was used in the assessment. Section 2.1.2 describes the PBPK model input parameters for the derivation of occupational exposure estimates. Section 2.2.3 describes the PBPK model input parameters for the derivation of consumer exposure estimates. Section 3.2.2 describes how PBPK-derived internal doses were used to determine PODs. Appendix I includes a description of both the rat and human PBPK models.
4	Several public commenters and peer review panelists noted that EPA's small shop focus may not be warranted, suggesting that statements about lack of glove use at small shops and the assumption that the small shops have exposures that are less	EPA/OPPT improved the focus descriptions in the Executive Summary, sections 1.1.1 and 1.1.3. EPA/OPPT found that there were limited readily available data to support the original assumption and removed the assumption that small shops have < 10 workers. Therefore, even though the interest is for small shops, the occupational exposure analysis retains data and analyses for all

	controlled and monitored than those seen in large-scale industrial operations are not well supported.	industries and shop sizes. EPA/OPPT cannot rule out that any of these industries may have small shops engaging in paint stripping jobs. In addition, EPA/OPPT revised the occupational exposure assessment to include a scenario approach that considers the use of respirators to control exposures. Section 2.1.1 contains information about the occupational scenarios examined in the final risk assessment.
5	Public commenters requested additional information to explain the use of different models in different work plan assessments.	The selection of exposure models for use in risk assessment depends on the data that are available for use in the exposure model. For example, MCCEM was used for DCM and NMP because there were chamber test emission data suitable for fitting this higher tier model. Data for use in MCCEM modeling were not available for TCE. Thus, E-FAST2/CEM were used in the TCE's consumer exposure model, as these models do not require emission data.
6	A number of public commenters suggested that the assessment is using screening-level methodology that may not be appropriate for risk assessment for regulatory decision-making (e.g., TCE, DCM and NMP)	EPA/OPPT disagrees with this comment. This assessment incorporates both measured data and modeling to estimate exposures under a number of different scenarios. For conducting Work Plan assessments EPA/OPPT may use a variety of appropriate available models to estimate parameters needed to calculate risks when measured data are unavailable. For example, EPA/OPPT has incorporated a revised PBPK model has been used to estimate internal doses, which allows for the effective use of toxicological data based on different routes of exposure for more robust dose-response assessments.
7	Public commenters noted that there was no clear framework to prioritize specific uses scenarios.	As described in section 1.2.3, EPA/OPPT considered the range of TSCA uses including petrochemical processing, engineering plastics, coatings (resins, paints, finishes, inks, and enamels), paint stripping, agricultural chemicals, electronic cleaning and industrial/ domestic cleaning. Narrowing of the scope required exclusion of some uses based on comparative judgments relative to paint stripping. These comparative judgments considered potential exposure among the primary uses identified (e.g., percent content relative to potential exposure).

		This assessment focused on the use of NMP in paint strippers because NMP with expected to have the highest potential exposures to both consumers and workers. In addition, NMP is a potential substitute for DCM in paint stripping applications, which was recently assessed as a work plan chemical. EPA/OPPT considered it prudent to evaluate NMP as a likely replacement.
8	Several commenters suggested that EPA/OPPT employ a systematic process for the evaluation of the quality of the studies used in the assessment.	EPA/OPPT used a systematic, weight of evidence approach to evaluating available data and data quality. EXPOSURE: For occupational exposure data, EPA has added descriptions of the literature search strategy and quality criteria to Appendix D. Section 2.2 and Appendix E now include a more detailed description of the approach taken to developing consumer exposure estimates. Consumer exposure data is extremely limited. No measurements of the concentrations of these chemicals from actual use by consumers in their homes are available. Also, no emission data are available for consumer products. A chamber study conducted by MRI (EPA, 1994), although there were calibration errors that had to be investigated, was deemed sufficient for estimating NMP air concentrations from paint stripping activities. Usage amounts came from survey information cited in EPA's Exposure Factors Handbook (EFH) (EPA, 2011) and to a small degree from other surveys. The data in the EFH has previously been peer reviewed. HAZARD Section 3.1 describes the approach and methodology EPA/OPPT used to evaluate toxicity data. Appendix F includes a description of literature collection, data quality evaluation and study selection. In summary, publicly available toxicity data were identified, starting with a survey of existing assessments. Additional studies suggested by peer reviewers and public

		commenters were added. Outcomes were evaluated for sensitivity and consistency. This resulted in the selection of developmental toxicity endpoints as the basis for the risk assessment.
9	One commenter suggested that EPA address OSHA authorities to regulate occupational exposures.	EPA/OPPT consulted with OSHA and NIOSH during the development of the NMP risk assessment. OSHA and NIOSH comments and suggestions were incorporated into the final risk assessment.
10	One public commenter suggested that the risk assessment should be classified as a Highly Influential Scientific Assessment (HISA)	This assessment was identified as an Influential Scientific Product (ISA). The peer review process for this ISA product was not different from that prescribed for a HISA.
11	Several commenters expressed concern that many of the documents cited in the risk assessment are not in the public domain.	EPA/OPPT encourages owners of studies and reports considered to be confidential business information to release as much information as possible. All of the data that form the basis of the quantitative risk assessment are from public sources.
12	Exposures should be estimated for women and children, including female children aged 16 - 21.	The selection of the lifestage of interest was driven by the identification of the most sensitive hazard endpoints (section 3.1.3.4). Although EPA/OPPT identified a number of hazard concerns (e.g., reproductive toxicity, neurotoxicity, liver and kidney toxicity), developmental endpoints were the most consistent, robust and sensitive. Therefore, pregnant women and women of childbearing age who may become pregnant, were selected as a focus for the risk estimates (section 4.1). However, EPA/OPPT considered potential risks to other lifestages and subpopulations, based on concern for other endpoints, but assumed that exposures that do not result in unacceptable risks for these particular lifestages would also be protective of other receptors, including children and adult males (section 4.1).
13	EPA should make an attempt to estimate oral exposure and incorporate the data into the aggregate exposure analysis if possible. If there are no data, this should be clearly identified as a data gap that could result in an underestimation of exposure.	EPA identifies in the section describing uncertainties (4.3) that exclusion of oral exposure will underestimate exposure, but this underestimation is not expected to contribute significantly to aggregate exposure, given occurrence and use patterns.

Worker Exposure Assessment

Charge Question 2-1: Please comment on the approach used and provide any specific suggestions or alternative approaches, models or information that should be considered by the Agency for improving its assessment of the workplace inhalation exposure, including specific citations (if available) of data sources characterizing occupational inhalation exposures.
Charge Question 4-1: Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of the workplace dermal exposure, including specific citations (if available) of data sources characterizing occupational dermal exposures. Please comment on the strengths and weaknesses of the evaluation and the choice of assumptions/input parameters for generating estimates of the NMP's dermal exposure.
Charge Question 4-2: Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of the consumer dermal exposure, including specific citations (if available) of data sources characterizing dermal exposures in a residential setting. As part of the review, please comment on the strengths and weaknesses of the evaluation and the choice of assumptions/input parameters for generating estimates of the NMP's dermal exposure.
Charge Question 4-3: Please comment on the assumptions used by the Agency regarding film thickness for the assessment, including any additional data on film thickness with which to assess dermal exposure to NMP for both consumers and workers.

#	Summary of Peer Review and Public Comments for Specific Issues Related to Charge Questions 1-1 and 1-2	EPA/OPPT Response
14	Panel members suggested that the literature search strategy should be described and recommended additional references as containing potentially relevant exposure data. Also, a public commenter asked why the occupational exposure assessment did not consider exposure monitoring data for graffiti workers reported in WHO (CICAD document).	EPA/OPPT has added descriptions of the literature search strategy and quality criteria to Appendix D EPA/OPPT reviewed the additional exposure-relevant references recommended by the public and peer review panel. The WHO data are included but have been expanded to include more data from the WHO primary references (Anundi et al., 2000; Anundi et al., 1993). A small amount of new inhalation data was identified, but all values were within the ranges of the original data sets. The additional data have been added to the data sets in Appendix D.

15	Regarding worker dermal exposure modeling and parameters, several issues were raised: a) Lack of consideration of glove use, particularly since dermal exposure estimates may not represent real world conditions based on the corrosive properties of NMP. EPA's assessments should be based on intended uses in accordance with label instructions. b) Differences in dermal exposure between the residential applicator and the worker applicator are substantial with the reason not clear, including film thicknesses. Also, one episode of dermal contact/ day is not conservative and is an uncertainty. Some parameters only use a single value that is too conservative. c) A sensitivity analysis of film thickness parameters and surface density is needed. (This comment also applies to the consumer exposure assessment)	a) Literature information on gloves and prevalence of their use has been presented, characterized and used for the dermal analyses in Appendix D. The updated assessment corrects the original erroneous statements indicating NMP as corrosive. EPA's assessments are based on intended uses in accordance with label instructions but also take into account scenarios where label instructions, particularly regarding use of gloves made of optimal material for protection against NMP are not followed as survey data has found applies to a significant fraction of workers. b) and c) The models used have changed from thin film to PBPK, reducing the number of parameter inputs. Two highly uncertain parameters, film thickness and number of episodes of dermal contact/ day are no longer used in the assessment. Dermal uptake is predicted based on the surface area exposed, concentration of NMP in contact (assumed to be equal to the formulation) and permeability constant which was derived from human PK studies. While dermal uptake is very sensitive to these parameters, the degree of uncertainty in them is fairly low. The fraction of total absorption by this route depends on the particular scenario and particularly glove use. The parameters have been harmonized for workers and consumers except for scenario specific differences in duration of contact and NMP concentrations in products. These differences are explained in Appendix D and E. And EPA has improved upon the composite range approach by including statistical values (e.g., 50th percentile, arithmetic mean) where possible. When statistical values cannot be provided, midpoints are provided as central tendency substitutes along with ranges.
16	Regarding worker inhalation monitoring data and its use in generating ADCs, several interrelated issues were raised:	a) EPA/OPPT further considered IMIS data and found no solid criteria for determining which IMIS data are associated with use of NMP-containing strippers. Thus, EPA has concluded that the original preference for literature data over IMIS is valid. EPA/OPPT has bolstered the text in Appendix D indicating that the IMIS data are excluded from use in risk estimation since

	a) More OSHA IMIS data should be used for estimating risks. b) Reliance on graffiti workers as the sole source of workplace exposure concentrations creates a large uncertainty and potential for underestimation of exposure. c) Data presentation and transparency should be improved, including being more statistical, using central tendencies, or developing a probabilistic approach rather than using only composite ranges. Exclusion of some data shown in the appendix is not clear. d) Exposure controls are neglected.	literature data were available and preferred due to their known applicability to paint stripping, while IMIS data may not be due to NMP-based strippers. b) EPA/OPPT has broadened the data used and created two assessed populations in the assessment. These populations are expected to cover the entirety of categories of workers who may be exposed to NMP-based strippers and NMP-based graffiti remover products. c) Data presentation, transparency, statistics (including central tendencies) and exposure controls are particularly interrelated for assessment purposes. EPA/OPPT has improved on the composite range approach by including statistical values (e.g., 50th percentile, arithmetic mean) where possible. When statistical values cannot be provided, midpoints are provided as central tendency substitutes along with ranges. EPA/OPPT bolstered the data summaries in tables and text to include numbers of studies, numbers of data points and study dates, along with adding more data to the summaries for completeness. EPA/OPPT determined that modeling or probabilistic approaches are inappropriate for this assessment due to the lack of statistical data for most of the parameters. These issues are discussed in Appendix D. Also, some previously excluded data have been included. The remaining excluded data are discussed, but these exclusions have no impact on the risk analyses. d) EPA/OPPT has included model runs with and without respirators and gloves. The relative prevalence of use of personal protective equipment is not known to EPA/OPPT. Readily available data were insufficient for quantifying exposure impacts due to other exposure control measures such as local ventilation, although anecdotal examples of such controls, where available, are included in the discussions in Appendix D.

17	Peer review panel members suggested that the assessment does not adequately address occupational non-users of NMP.	The updated risk assessment clarifies exposure issues for occupational non-users. Section 2.1.1.2 describes the general approach. Section 2.1.1.3 explains that each exposure scenario also included a nearby worker not directly working with NMP (non-user), who was assumed to not be wearing a respirator but to only have incidental dermal contact equal to 1% of the skin area.
18	Public commenters suggested that the US census data are too weak to be used to calculate worker population estimates.	EPA/OPPT considered other data sources such as EPA's National Emission Standards for Hazardous Air Pollutants (NESHAP) for Paint Stripping. NESHAP data were usable for postulating estimates of the total population of workers involved in the DCM-based paint stripping operations for all industries combined. This estimate for DCM-based stripping was assumed to be an upper bound for NMP-based stripping. Please see Appendix D for further discussion. EPA/OPPT also made revisions to Appendix D to clearly show the estimates of number of workers per shop in each of the industries.
19	A public commenter asked why the occupational exposure assessment did not consider the use of NMP-based graffiti removers by other occupations.	Data for other such occupations were not found. The updated assessment notes in Appendix D that such occupations may have exposures but these would be expected to be lower than the exposures of those whose occupation is graffiti remover.
20	A public commenter asked why the occupational exposure assessment did not consider other NMP-based paint strippers.	EPA/ OPPT is not aware of other NMP-based paint strippers that are not considered.

21	A peer review panelist requested that EPA/OPPT include more information on label instructions, common industry practices and high-end or extremes in stripper use. Also, a public commenter requested that a more robust description of the assumptions made regarding PPE and gloves in the occupational setting be included in the assessment.	Appendix D incorporated additional information about common industry practices when available. EPA/OPPT could not find data on high-end and extreme stripper use rates. Information on labeling instructions was not incorporated in the final risk assessment because such instructions would be anecdotal. With the exception of respirator use, all of these types of information and data suggested for inclusion would not impact exposure estimates used in the risk analyses. The expected prevalence of respirator use and gloves are discussed qualitatively in Appendix D.
22	Discussion of uncertainties and limitations should be improved for the worker exposure assessment. Directional impact on risk should be included and the discussion should be more complete and robust.	EPA/OPPT determined gaps in the discussion and completed improvements in section 4.3.1, including to directional impact on risk when possible and also making the discussion more complete and robust.

Consumer Exposure Assessment

Charge Question 3-1: Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of consumer inhalation exposure, including specific citations of data sources characterizing consumer emission profiles of NMP-based paint strippers. As part of the review, please also evaluate the sensitivity analysis conducted for the assessment and comment on the strengths and weaknesses of the evaluation of different exposure scenarios and the choice of assumptions/input parameters for generating central tendency and upper-end NMP air concentrations.

#	Summary of Peer Review and Public Comments for Specific Issues Related to Charge Questions 1-1 and 1-2	EPA/OPPT Response
23	A panelist suggested expanding the paint stripping protocol description and insert same in body of document.	As stated in section 2.2.1.2 of the body of the report, Section E-3 of Appendix E discusses label instructions for ventilation and user location during the wait period. The application method and times per step are described adequately for the zone modeling that is used. Additional considerations such as effects of containers left open, methods to loosen paint and cleanup procedures did not have available data sufficient for quantification.
24	A peer review panelist and a public commenter stated that the presentations in Table 3-7 and D-4 for user and non-user are confusing.	The confusion results because the scenarios are labeled as upper-end for the user or non-user based on changes in parameters shown to be more sensitive for the user or non-user—this does not mean that the results are not upper-end for the other exposure group. For example, all of the scenarios where the most sensitive parameters for the non-user were made upper-end resulted in exposures for the user that were higher than the scenarios run as upper-end for the user; this is because the effect of higher chemical mass plus low rest-of-house ACH to increase exposures for the user was greater than the lower-exposure impact of user location in rest-of-house instead of workshop (the user location was the most sensitive parameter for short exposures but much less sensitive at longer exposure times). EPA/OPPT has edited the tables, now table 2-4 and 2-5 and their associated text in sections 2.2 to clarify these points.

25	A panelist and public commenter stated that the Executive Summary and toxicology sections present contradictory information regarding NMP corrosivity; one states that it is corrosive, the other that it is an irritant, but not corrosive.	The hazard summary has been revised to state that NMP is not corrosive. See section 3.1.2.
26	A peer review panelist commented that the role of human behavior in responding to irritating substances by increasing ventilation, leaving the area, or other actions does not seem to have been incorporated in extreme exposure scenarios or models.	EPA/OPPT assumes that this comment is related to the incorrect description of NMP as corrosive. As discussed in the response to comment 15, the corrosive description has been corrected in the revised assessment. Note that in the extreme exposure (because of large tub area, low ventilation and small zone volumes) bathtub stripping scenarios that the user leaves the work area during the wait period.
27	A peer review panelist pointed out that there is a discrepancy in the reporting of the vapor pressure in Table 2-1 versus Table D-6.	EPA/OPPT will only refer to the peer reviewed value of 0.19 mmHg at 25°C that was in Table 1-1 (previous Table 2-1). The MCCEM saturation concentration scenarios affected by this change have been revised in the final assessment.
28	A public commenter stated that EPA/OPPT's assumptions for the importance of volatilization are internally inconsistent. NMP was developed as a low-volatile alternative to methylene chloride for paint stripping applications. Volatilization of NMP is not expected to be significant during normal use. Based on its Henry's Law constant ($4.45X10^{-8}$ atm-cu m/mole), NMP is expected to be essentially nonvolatile from water and soil (HSDB, 2012). This conclusion is consistent with the results of the fugacity modeling presented in Table 2-4 of EPA/OPPT's draft assessment, which indicate that only 0.1% of NMP released to the environment will be	The release fraction of 0.26 for brush-on NMP is the theoretical upper bound of the release over an infinite period of time based on measured concentration data collected during chamber studies in EPA (1994). The assessment states that about 4.7% (a 0.047 fraction) of the brush-on NMP would be released in three hours, which is the scenario with longest time frame. Emissions are truncated at the end of the scenarios because scrapings are assumed to be removed from the house. Also, the EPA (1994) chamber data were collected over approximately a 4.5-hr period for the brush-on stripper. Because modeled emissions in all cases are over a shorter time period than the collected measurement data, there is a high degree of confidence in the emission profiles used in the modeling study. In addition, the comparison of these predictions to fugacity estimates must be made with caution due to the underlying assumptions of each

	found in air. In contrast, EPA/OPPT has assumed air release fractions of 0.26-0.52 for NMP during normal use (i.e., 26-52% of the mass of NMP applied will volatilize during use.	method. The fugacity model is predicated on equilibrium, with the Level III model incorporating steady-state behavior together with multimedia transport. The modeling study used a dynamic mass-balance model, incorporating time-varying emission rates and accounting for transport and removal processes. The fugacity ratio of 0.1% assumes transport rates that are almost certainly different than those assumed in the modeling study.
29	A public comment stated that all the exposure scenarios were indoor and asked whether there was consideration of product use outside.	It is correct that the assessment is of indoor use only, so the assessment exposure descriptors refer only to a range of indoor exposures. The risk assessment was edited to more clearly reflect this.
30	A peer review panelist suggested that monitored radon concentration differences according to floor of home could be used as a check of ROH estimates in consumer inhalation modeling for non-users.	EPA/OPPT does not think that the suggested radon concentration ratios are appropriate for the NMP analysis because they are slowly changing, virtual steady-state conditions, whereas the stripper use generates rapid changes in NMP concentration.
31	A peer review panelist and a public commenter suggested that differences in worker and consumer dermal exposure scenarios should be harmonized or better explained.	EPA/OPPT has developed a harmonized approach to replace the original worker and consumer dermal exposure scenarios.
32	Peer review panelists and a public commenter suggested that the consumer inhalation modeling results be compared to data from the MRI and occupational exposure studies.	Comparison of the MCCEM results to the MRI study results was complicated by an apparent discrepancy between the concentration values reported in graphical plots versus those for the same test reported in time-integrated tables; this is discussed in section D.1 of Appendix D of the revised assessment.
33	A peer review panelist commented that the EPA 1994 chamber test of consumer exposures is referred to as an occupational study in that section of the assessment—it	EPA/OPPT acknowledges this error and has incorporated the recommendation.

	should be referred to consistently as a chamber test throughout the report.	
34	A peer review panelist commented that the consumer application and scraping times seem unrealistically low. Since they were derived from a chamber test using flat panels they do not account for more intricate work pieces; perhaps doubling the application/scrape times could be used for upper-end scenarios.	As stated in the *Stripping Sequence* of the Inhalation Exposure Scenario Inputs section of the Consumer Exposure Assessment Appendix E-3, the application and scraping times were assumptions that fit the overall times reported for the EPA (1994) scenarios. It is possible that these times could be greater or smaller by an unknown amount; however, the stripping sequence was done twice for all scenarios, thus doubling all the exposure times. Also, because the sensitivity analysis indicated that User Location was the most sensitive exposure parameter, one of the upper end workshop scenarios designated the wait location of the user to be in the room-of-use, so the user was exposed to the NMP concentrations within the workshop for the entire stripping period (apply/wait/scrape).
35	A peer review panelist commented that there is evidence in the Riley et al. (2001) survey that a substantial proportion of users do not open windows. Sensitivity analysis shows that workshop ACH is a strong determinant of user and non-user exposures, so consider extra scenarios with closed windows (lower ACH in room of use).	Excluding the users in other locations or with ventilation, the Riley et al. (2001) survey indicated approximately 20% of users are indoors without open windows. Regarding the impact of the workshop ACH—it is less sensitive than user location, chemical mass and rest-of-house ACH. With the exception of the bathroom scenario, which replicates very low ventilation conditions from an actual DCM stripper scenario so NMP exposures can be compared under those conditions, all the consumer scenario parameter choices are supported by label suggestions for ventilation (open windows) and/or by preponderance of information on indoor user behavior in (Abt Associates (1992); Pollack-Nelson (1995)) and Riley et al. (2001). This information is presented in detail in the Inhalation Exposure Scenario Inputs section of Appendix E-3: Consumer Exposure Assessment
36	A peer review panelist commented that the spray-on product is only modeled in workshop scenarios; consider adding another scenario for use of spray-on product in the bathroom.	EPA/OPPT has edited the spray-on product scenarios for the revised assessment, primarily because the MRI chamber tests ((US EPA, 1994) that served as a basis for emission profiles did not include any applications involving NMP-containing spray-on strippers. Given the assumptions used for the spray-on scenario, expanded modeling was not performed.

		Emission parameters for the spray applied product were not available, so upper and lower estimates were developed to estimate exposures. The lower estimate was based on the brush applied data and the upper estimate was set as ten times higher based on professional judgment for the relationship between brush and spray applied products. The uncertainty of these estimates precludes performing a highly refined estimate as reliable input data is a prerequisite for a detailed modeling assessment. Thus the spray scenario is presented as an estimate of potential exposures.
37	A peer review panelist commented that use of the term "application rate" for g/ft^2 is confusing because rate implies the pace (amount per time frame), whereas this is the amount per surface.	Although in the exposure assessment field rate typically represents the ratio of a mass or quantity to time (e.g., emission rate or air flow rate), rate is more generally defined as the ratio of one quantity against another. Therefore the use of rate to describe mass per area is correct, as is the use of rate to describe mass per time. The report is careful to define the units in places where the term can be confused; as there is no better terminology for amount of product applied per area, the use of the term is appropriate.
38	A peer review panelist commented that dermal exposure should be estimated separately for women, using female-specific body weight and hand size.	EPA/OPPT has adopted this recommendation.
39	A peer review panelist commented that the consumer dermal analysis would be improved by a more formal set of distributional representations of variability and uncertainty.	The consumer dermal analysis applies all the available distributional data (NMP product weight fraction and density), but considerable uncertainty remains in the factors lacking data that are based on professional judgment (exposed skin surface area and frequency of exposure). Reducing this uncertainty by acquiring data that is representative of the distributions for these parameters is beyond the scope of this assessment.
40	A peer review panelist requested an explanation of the differences in hand surface areas and film thicknesses between worker and consumer dermal exposure assessments.	In the revised assessment the worker and consumer user dermal scenarios have been harmonized across common exposure factors, such as hand surface area.

41	a) A peer review panelist commented that a probabilistic approach could prove much more informative than the varying point estimate approach used for consumer inhalation assessment. It would be useful to clearly state which risks would not occur or be less likely if recommended safety precautions were taken. b) A peer review panelist and a public commenter recommended using Riley et al. (2001) and Abt Associates (1992) survey data to present information on degree of consumer compliance to manufacturer instructions. c) A public commenter stated that some of EPA/OPPT's estimated air concentrations are bounding; also, air modeling is not needed for assessing consumer inhalation exposures—compare to monitoring data. d) A public commenter recommended that EPA/OPPT construct scenarios based on recommended product use and labeling precautions, not on product misuse, suggesting that EPA/OPPT has overstated risk via the use of worst case scenario assessment.	a) A probabilistic approach would be a higher tier (more sophisticated) effort that requires additional input data that are currently not available. b) With the exception of the bathroom scenario, which replicates very low ventilation conditions from an actual DCM stripper scenario so NMP exposures can be directly compared under those conditions (which are characterized as high-end to bounding), all the consumer scenario parameter choices are supported by label suggestions for ventilation (open windows) and/or by preponderance of information on indoor user behavior (Abt Associates, 1992; Pollack-Nelson, 1995; Riley et al., 2001). However, these references are not NMP-specific, so degree of compliance or other quantitative details cannot be determined from them. More details are presented in detail in the Inhalation Exposure Scenario Inputs section of Appendix E-3: Consumer Exposure Assessment. c) The characterization of the bathroom scenarios is high-end to bounding because it replicates a DCM CDC/NIOSH case. This scenario was included here if NMP is selected as a substitute for DCM by consumers. However, the workshop scenarios were designed to be considered plausible, in fact, the upper end amount of stripper product used in the assessment is only about the 80th percentile value from the Abt Associates (1992) survey, so yields a lower exposure estimate than the higher amounts from that survey. The higher amounts were not used because their occurrence is less likely, so the resulting scenarios would be considered less plausible. d) All the consumer scenario parameter choices are supported by label suggestions for ventilation (open windows) and/or by preponderance of information on indoor user behavior in Abt Associates (1992), Pollack-Nelson (1995) and Riley et al. (2001). The scenarios evaluated considered use with and without PPE.

42	A public commenter stated that if users took breaks outside, as mentioned in the assessment on page 109, it is not clear why this scenario was not modeled.	The referenced sentence on page 109 of the draft assessment presents examples of break activities mentioning both indoor, e.g., making a sandwich in kitchen and outdoor, e.g., yard work, activities. The revised assessment makes clear that it is an indoor assessment only.
43	Public commenters made the following suggestions: a) EPA/OPPT should use the appropriate body weight from EPA's Exposure Factors Handbook for target population of women of child-bearing age and discuss effects to infants and children. b) Justify the differences of hand's surface area and thin film contact between consumers and workers. c) EPA/OPPT should include other possibilities than just one thin film with each exposure event.	a) In the revised assessment, harmonized worker and consumer dermal exposure scenarios shared common exposure factors, e.g., body weight, hand size. Selection of these parameters are justified in the document. b) Since the risk assessment was based on fetal effects, the exposure assessment focused on women of childbearing age and pregnant women. Since there are other hazard endpoints of interest (section 3.1.2), the risk characterization also discussed potential concerns for other lifestages and subpopulations, but concluded that EPA/OPPT expects risks to these lifestages and subpopulations to be lower, for a variety of reasons. See sections 3.2.5 and 4.1 for specific details. c) The occupational assessment assumes that the scenario-specific surface area for liquid contact is exposed to the liquid for the entire time that the worker is on the task. For the full work-day exposure this is two periods of 4 h separated by a 30-min lunch break. The concentration in the liquid is assumed to be constant at the formulation concentration for the entire time. So it is not assumed that a single "film" is applied at the beginning of exposure and no more is deposited.
44	A public commenter urged EPA/OPPT not to use the professional judgment value for the thin film thickness used in the consumer exposure assessment; instead, use the less conservative approach used for the worker exposure estimates.	The revised assessment has harmonized occupational and consumer dermal assessments and uses the concentrations of NMP (weight fractions) identified by surveying MSDS's of NMP-containing paint strippers for both worker and consumer exposure estimates.
45	A peer review panelist recommended that the consumer inhalation modeling be redone	The response to this comment merits a detailed explanation of the approach used to estimate consumer inhalation. Please see the Extended

	because the derivation of the emission rates was done incorrectly. More specifically, the panelist suggested that the parameters used for the emission rate modeling reported in Table D-3 of the NMP Risk Assessment document are incorrect and cannot be used to obtain the results shown in Figure D-5 and that the k value for the first exponential is unrealistically high.	Response to this comment, titled "NMP Memo FINAL – Response to Armstrong Comments 18Feb2014" included in the public docket (Docket: EPA-HQ-OPPT-2012-0725).
46	A peer review panelist recommended that the modeling for the bathtub stripping scenario be based on either a different modeling equation than that in the MCCEM model, or on emission rates from appropriate lab scale experiments. This recommendation is based on the following: the MCCEM model that is properly fitted to MRI emission data should be appropriate for flat surface scraping, but the commenter states that a thin saturated NMP vapor layer, i.e., "backpressure," due to the concave shape of bathtub is not adequately represented by the flat surfaces in the MRI chamber test, so it is likely that the MCCEM modeling significantly overestimates the NMP concentration in air.	EPA/OPPT acknowledges that there is uncertainty about the application of the emission factors derived from the flat panels in the MRI chamber test to the concave surface of a bathtub. However, it is not clear that a backpressure condition would occur or have a significant impact, for the following reasons: 1) the majority of the paint stripping time for a tub (64%) consists of user brush-on and scraping of the stripper, which would create air turbulence disrupting conditions necessary for backpressure, 2) MCCEM predicts that NMP concentrations in the source cloud would be at the saturation concentration for almost the entire stripping time, so a small decrease in mass-transfer rate might delay reaching the saturation concentration but have a negligible impact after saturation was reached, 3) the source cloud assumption is based on estimates of room airflow velocities. If the surface velocities are expected to be low, such that a boundary layer inhibits mass transfer, this would imply that the source-cloud ventilation would also be lower, tending to increase the NMP concentrations in the source cloud. The uncertainties in these parameters may very well dwarf the potential impacts of low air velocities and subsequent backpressure layer formation. Monitoring of NMP concentrations in targeted laboratory or field studies would best address the potential impact of a backpressure layer, but are beyond the scope of this assessment.

47	A public commenter noted that the sensitivity analyses are presented for model predictions for 1-hour and 24-hour averages. Because neither of these time points is used in the risk assessment, EPA/OPPT should present sensitivity results corresponding to the 4-hour predictions used in the risk assessment.	The updated risk assessment relies on PBPK modeling that uses 24 hours of indoor air data generated by the exposure model (MCCEM). For the workplace scenario the internal dose metric used is the (average) 24-hour blood AUC and for the consumer scenarios the internal dose metric used is the peak blood concentration (C_{max}). Therefore the sensitivity analysis was performed for the 1 hour and 24 hour averages. Sensitivity of the 1 hour average was also evaluated since it is more representative of peak blood levels for residential uses.
48	A peer reviewer recommended a correction to the near field (source cloud) assessment for bathtub scenario and further recommended that all the inhalation modeling utilize the near field approach; also, that there be an expanded discussion of the MCCEM model.	The source cloud (near field) mathematical error and associated exposure estimates have been corrected for the bathtub stripping scenario; however, near field modeling was not considered as appropriate in the workshop consumer exposure scenarios, so this was not done. Please see extensive discussion in Appendix E, section E-3.
49	A peer review panelist commented that the bathtub scenario did not consider use of an exhaust fan.	As stated in the Description of Exposure Scenarios portion of Section 2.2.1.2 of the risk assessment, the bathtub stripping scenarios were developed to simulate use conditions similar to those reported in a CDC/NIOSH occupational-exposure case for a DCM-containing paint stripper (CDC, 2012a, 2012b); an exhaust fan was not used in that case. The designation of no fan use for these scenarios is also presented in Table 2-5.
50	A public commenter urged EPA/OPPT to not rely on saturated vapor concentrations for the worst case inhalation scenario, because saturation typically only occurs under experimental conditions. Instead, assume the EPA 1994b study's monitoring data as worst case.	The upper end to bounding bathtub stripping exposures are from a scenario that replicates an actual CDC/NIOSH case for DCM use. The greater stripper amount and lower ventilation and room of use volume for the bathtub scenario than the chamber test make it a more conservative scenario. The two different bathtub scenarios reflect changes in plausible humidity levels, which have a substantial effect on NMP volatilization, so should be in the assessment. If left out, the predicted exposure levels would have been even higher.

51	A public commenter noted that NMP-based products are often formulated with other organic solvents that could increase dermal absorption; this should be discussed.	The revised risk assessment discusses this uncertainty in the dermal absorption rate (see Section 4.3) but does not attempt to quantitatively estimate the effect of different solvents on skin absorption of NMP.
52	A public commenter suggested discussion of use of various other NMP-based products, e.g., graffiti removers, by custodial staff and public works employees.	The assessment of risks to workers associated with the use of graffiti removers was included in this risk assessment.
53	A peer review panelist and public commenters suggested that the assessment be revised to address inhalation and dermal exposures as a combined total dose.	The revised assessment includes PBPK modeling of the combined inhalation, dermal and vapor-through-skin exposures.
54	Public commenters recommended that EPA/OPPT should attempt to estimate oral exposure to NMP in pesticides used for food crops, because NMP is allowed unregulated in pesticides applied to food.	Estimating and adding this exposure is beyond the scope of this assessment.

Hazard/Dose-Response Assessment

Charge Question 5-1: Please comment on EPA's use of the identified developmental studies and POD to assess acute inhalation exposures to NMP use in paint strippers. As part of the review, provide your input on the appropriateness of using an acute POD based on fetal body weight decrements that were observed in the presence of maternal body weight decrements following exposure to NMP during gestational days 6 to 13. Please comment on whether the maternal no-observed-adverse-effect level (NOAEL) of 122 mg/m3 (Saillenfait et al. 2001, 2003) should be analyzed in the MOE calculations along with the fetal body weigh decrements. Please specify any other endpoints that should be considered for the hazard evaluation of acute inhalation exposures. Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.

Charge Question 6-1: Please comment on EPA's use of the identified developmental studies and POD to assess chronic inhalation exposures. As part of the review, please comment on the appropriateness of using a developmental toxicity endpoint and the identified effects to assess chronic inhalation exposures to NMP-based paint strippers. Please specify any other toxicological endpoints that should be considered for the hazard evaluation of acute inhalation exposures. Also, please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.

Charge Question 7-1: Please comment on EPA's use of the identified developmental study and POD to assess acute and chronic dermal exposures. As part of the review, provide your input on the appropriateness of using a developmental toxicity endpoint and the identified effects to assess acute and chronic dermal exposures to NMP-based strippers. Please specify any other endpoints that should be considered for the hazard of acute or chronic dermal exposures. Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.

#	Summary of Peer Review and Public Comments for Specific Issues Related to Charge Questions 1-1 and 1-2	EPA/OPPT Response
55	A number of public commenters and peer review panelists suggested studies that should be considered in the risk assessment. A public commenter suggested review of two additional studies that focused on male and female reproductive toxicity in rats.	EPA/OPPT incorporated the results of an expanded review of studies identified by commenters. The final risk assessment includes a discussion of studies that identify male and female reproductive effects. See section 3.1.2.
56	A peer review panelist indicated that human ethics reviews should be conducted for the	EPA/OPPT completed a human ethics review for each intentional dosing study used to support the PBPK model. The reviews are available in Appendix G.

	intentional dosing human studies used to support PBPK model.	
57	Several commenters requested additional information on the determination that reproductive toxicity was not the basis for the risk assessment. It was also noted that the draft report relied heavily and almost exclusively on a 2007 OECD SIDS Initial Assessment Report for NMP toxicological information. It did not cite or discuss different scientific opinions by EPA/OPPT, Cal/EPA, WHO and others related to information in the OECD report.	The final risk assessment incorporates information based on multiple toxicological reviews and includes consideration of a number of additional toxicological studies. In addition, the final risk assessment describes a range of hazard concerns, including reproductive toxicity, neurotoxicity and liver and kidney toxicity and explains the rationale for the selection of developmental endpoints as the basis for risk calculations.
58	EPA/OPPT should calculate how much parent compound and metabolites are remaining in the body after 24 hr exposure.	The metabolism of NMP is considered a detoxification and NMP metabolites are not known to have significant toxicity. NMP is rapidly metabolized *in vivo* with a half-life of approximately 2.5 hours. Therefore NMP is not expected to bioaccumulate. Some NMP metabolites may bioaccumulate in an individual repeatedly exposed to high doses but they are not expected to have adverse health effects.
59	A public commenter suggested that EPA/OPPT's use of dermal extrapolation methods (from rat to human data) was inappropriate. Specifically that EPA/OPPT did not take into account the innate difference in absorption rate of substances across rodent skin versus human skin, as described in the EPA Dermal Exposure Assessment guidelines (Interim Report) (EPA, 1992).	EPA/OPPT is now using PBPK modeling for the interspecies extrapolation. Specifically the rat and human dermal absorption parameters were obtained from species-specific pharmacokinetic experiments, so do represent the species-specific absorption rates. The human parameters also distinguish absorption for 100% vs. diluted NMP, which were observed to differ.

60	Several commenters suggested using benchmark dose modeling for deriving the POD. Several public commenters asserted that the minimal effects on fetal body weight do not warrant use of BMR of 5% and instead recommended the use of a BMR of 1 SD. One public commenter recommended the use of a BMR of 1SD (approximately 7.7%) for fetal BW effects based on the combined control data reported by the Saillenfait studies (Saillenfait et al., 2002; Saillenfait et al., 2003) where the mean and standard deviation (SD) are 5.70 g and 0.44, respectively. A peer review panelist recommended the use of a BMR of 1%	EPA agreed that the BMD approach was most appropriate for derivation of the POD, when the data supported this approach. A BMR of 5% decreased fetal body weight was used because in the absence of knowledge as to what level of response to consider adverse, it has been suggested to consider a 5% change relative to the control mean for developmental endpoints (Kavlock et al., 1995). A BMR of 1% was used for increased resorptions/fetal mortality to address the relative severity of this endpoint (EPA, 2012). BMD modeling results for a BMR of 1 SD are presented for comparison in the BMD analysis Appendix H. A BMR of 1% for increased resorptions/fetal mortality was used to address the relative severity of this endpoint (EPA, 2012).
62	A peer review panelist suggested that the selection of an acute POD based on a developmental toxicity study is overly conservative. Citing Van Raaij et al. (2003), the commenter suggested that the average NOAEL from repeat dose studies is 3.4 times higher and the average LOAEL is 4.76-fold higher in the single (acute) studies. The commenter recommends that this analysis supports the use of 2- 4-fold factor in going from the rat developmental studies to an	The revised risk assessment considers a different set of endpoints for the calculation of risks associated with acute exposures. Specifically, EPA/OPPT focused on increased resorptions, fetal mortality and skeletal malformations, as these endpoints are more plausibly associated with short-term (acute) exposure periods (Van Raaij et al., 2003).

	acute POD rather than the conservative no adjustment approach.	
63	A peer review panelist questioned Selection of BMD models, noting that the model with the lowest AIC was not always selected.	The benchmark dose modeling has been revised for the selection of PODs for both chronic and acute exposures. Of the models that fit the data adequately (chi-square goodness of fit p-value) and when the BMD:BMDL ratio was less than 3 for all adequate models, the best fitting model was selected based on the model with the lowest AIC value.
64	A number of commenters questioned the basis for the calculation of PODs used in the draft risk assessment: A public commenter suggested that decrements in fetal body weight should not be used to set the POD for acute exposure risk calculations. A public commenter recommended the use of a quantitative risk assessment approach to identify hazard values for NMP that is consistent with the approach used by Cal/EPA Limit. A public commenter criticized the use of the Becci et al. (1982) study for the derivation of the POD, indicating that in the study the rats were dermally exposed to NMP during gestation days (GD) 6-15, an exposure duration that is inconsistent with the longer exposure period (GDs 6-20) of current guidelines and does not permit an adequate	In the revised risk assessment, EPA/OPPT considered a wider selection of studies and analyses than in the original assessment. The selection of studies for the basis of the risk calculations considered the appropriateness of endpoints for the different exposure durations and scenarios and the consistency of outcome among the different studies. The revised risk assessment for chronic exposure is based on decreased fetal body weights, observed in the DuPont (1990), Saillenfait et al. (2002), Saillenfait et al. (2003) and Becci et al. (1982). The POD is based on the BMR of 5% from Saillenfait et al. (2003), which EPA/OPPT judged to be the most sensitive and robust of the studies. The revised risk assessment for acute exposure is based on fetal resorptions, observed in Saillenfait et al. (2002), Saillenfait et al. (2003) and Becci et al. (1982). The POD is based on the BMR of 1% from the combined Saillenfait et al. (2002) and (Saillenfait et al. (2003)), which resulted in a similar effect level, that EPA/OPPT judged to be the most sensitive and robust of the studies. While maternal stress has been noted in some studies, EPA guidance (EPA, 1991) precludes using maternal stress to discount fetal effects.

	characterization of the developmental endpoints. A public commenter asserted that incomplete vertebral ossification (Becci et al., 1982) is an inappropriate endpoint for repeated dose toxicity. EPA/OPPT should instead use fetal body weight reported by Saillenfait et al. (Saillenfait et al., 2002; Saillenfait et al., 2003). A public commenter suggested that the acute BMDL05 for skeletal malformations should be based on the pooled Saillenfait (2002; 2003) data, without the result at the highest internal dose where extreme toxicity was noted. A public commenter recommended against pooling the fetal BW of Saillenfait and Becci due to maternal stress factors. EPA should use the inhalation fetal BW as a health protective POD	
65	A peer reviewer noted the absence of epidemiological data and asked if epidemiological data were included in the literature search.	A single case report was identified (Solomon et al., 1996). The study was included in the hazard identification and weight of evidence discussions.
66	Several commenters noted errors in the exposure section of the draft risk assessment:	a) This sentence is removed and a more informative description of absorption via dermal and inhalation exposures is given in section 3.2.2.

	a) pp. 44-46*:* Statement that dermal exposure is "(≤100 %) depending on conditions" is not very informative. The contrast with the 40-60 percent range given for inhalation exposures seems to imply that dermal is more efficient than inhalation exposure in leading to absorption. This implication should be removed. b) p. 151*:* Caption to Figure F2 refers to data in Table D-1 when it should be F-1. c) pp.152-3 Captions in the figures refer to dose in mg/m^3 but dose is actually stated in ppm. d) The plots show results of exponential models 2 and 3, but the AICs for the Hill and linear models are both listed as lower than these in Table F-2. The BMCL for the Hill model, with the lowest AIC is listed as 130.19—much less than the 300-odd mg/m^3 shown for the linear and exponential models 2 and 3 that appear to have been chosen as the basis of the BMD determination. e) Also, the final paragraph on page 45, reproduced here, seems incomplete: "It is interesting to note that there is evidence to support that absorption and effect are very similar by oral and dermal routes. Oral LD50	b) Figure F-2 – BMD Appendix plot of mean response by dose with fitted curve has been replaced by new BMD modeling (Appendix H). c) The captions in BMD modeling have been updated based on internal dose metrics with the appropriate units. d) The basis of BMD determinations for the updated BMD modeling are explained in the BMD Analysis Appendix H. e) The sentence comparing LD50 values across routes was removed. This section was re-written. f) All instances of the word rationale are now correctly spelled. g) The table of data in the BMD appendix H (Table H-1) was updated to correctly indicate the number refers to the number of litters examined and not number of fetuses.

	values were 4,150, 3,914 and 3,605 mg/kg in rats (Ansell and Fowler, 1988; Bartsch et al., 1976; BASF AG, 1963; as cited in OECD, 2007, respectively) and 7,725 and 4,050 mg/kg in mice (Bartsch et al., 1976; Weisbrod and Seyring, 1980; Weisbrod, 1981; as cited in OECD, 2007) to dermal dose levels." f) And on page 49, in this heading, "*Rational for Study and Endpoint Selection for Acute PODs."* "*Rational*" should be "*Rationale*." g) In Table F-1, the column heading refers to "fetuses," but the data are actually numbers of litters examined.	

Hazard Assessment: Use of PBPK Model

Charge Question 8-1: Please review the model and comment on the Poet et al. (2010) analysis as well as EPA's evaluation of the revised model. Please comment on whether the model is clearly and transparently described and technically and scientifically adequate for supporting OPPT's work plan risk assessment for NMP-based paint strippers. Specifically, please address the structure of the PBPK model, parameter calibration and model predictions of the available in vivo data.

Charge Question 8-2: Please comment on the appropriateness of using the selected dose metric for chronic inhalation and dermal exposures based on the maternal blood concentration of the parent compound expressed as the area under the curve (AUC). Please comment on whether the maternal dose metric is a reasonable surrogate for a fetal dose metric in the absence of fetal metabolism data.

Charge Question 8-3: Please comment on whether the selected dose metric for acute inhalation and dermal exposures should be reported as the maternal blood AUC of the parent compound and/or the maximum concentration (C_{max}) in maternal blood.

Charge Question 8-4: Please comment on whether the BMD analysis should be conducted with the PBPK-derived internal doses or the external air concentrations (standard approach) reported in Saillenfait et al. 2003. Please specify whether the BMD calculations (Appendix F of draft risk assessment) were appropriately conducted and documented.

#	Summary of Peer Review and Public Comments for Specific Issues Related to Charge Questions 8-1 through 8-4	EPA/OPPT Response
67	Several reviewers suggest that glove use and effectiveness of gloves should be discussed.	The PBPK model simulates scenarios where gloves are or are not used. EPA/OPPT evaluated a range of exposed surface area for brush-on application, 460, 665 and 890 cm^2, to represent the palm-side of two hands, the palm size of two hands and part of the back of hand, and both sides of both hands, respectively. EPA/OPPT assumed that the surface area was reduced by the glove effectiveness factor of 90% when appropriate gloves were used. The remaining (10%) exposed surface area is an approximation that is intended to account for accidental exposures outside of the hands, glove failure and ineffectual gloves. A nominal surface area of 1 cm^2 representing a finger-tip was assumed to become wetted for spray-on application. Again this is reduced by 90% when gloves are used.
68	A peer reviewer noted in one human exposure study (Bader and Van Thiel, 2006) the measured	Evaluation of individual subject data with the PBPK model found decreased amounts of NMP in blood *and* its metabolite 5HNMP in blood and urine. If metabolism had been induced, the amount of 5HNMP in blood and urine would have increased. Further, this

	NMP blood level AUCs relative to exposure concentrations were decreased, which might suggest induction of metabolism.	change only occurred in 4 of the 8 subjects. This evidence is not supportive of the proposed metabolic induction and may suggest differences in absorption. The PBPK model was refit to the low-concentration data to avoid under-estimating internal doses and adequately fits the data in to multiple data sets shown in the PBPK Appendix I.
69	A peer reviewer expressed concern about the adequacy of using the well mixed assumption for representing absorption of NMP in the skin during after dermal exposures.	The PBPK model was re-fit to the human dermal data sets. Specifically, the model has now been fit separately to data for neat vs. 50% diluted NMP, which exhibit different absorption efficiencies. Unfortunately blood levels of NMP were not measured during the human dermal studies, but blood and urinary 5-HNMP was. Fits to these data, shown in the PBPK Appendix I, are considered adequate and do not justify changes in the model structure. For NMP the clearance rate is more rate-limiting than absorption, so a detailed dermal model structure is not as important as for other chemicals.
70	Peer reviewers noted the method of calculating dermal absorption for workplace and residential exposures were different.	The PBPK dermal model is now applied in the same way to both workplace and consumer exposures.
71	PBPK model: Legacy code in model	A clean revised version of the PBPK model is included in the public docket (Docket: EPA-HQ-OPPT-2012-0725).
72	Peer reviewers noted absorption of 50% diluted NMP was less than neat NMP and suggested evaluation of the dermal absorption model with data from Akrill et al., 2002.	The PBPK model the permeability constant has now been fit separately to the neat and 50% diluted NMP blood and urine time course data (Akesson et al., 2004) since NMP diluted in water has reduced dermal absorption. Two other studies Akrill et al. 2002 and Kenner et al., 2007 have dermal exposures to NMP and measured total 5HNMP in urine. Comparison of these data with the PBPK model is discussed in the PBPK Appendix I. The mechanism of the nonlinearity in absorption is unknown there is not sufficient information to describe absorption across all possible dilution levels. The permeability for neat absorption was used to workplace applications involving undiluted NMP. The permeability estimated from 50% diluted NMP was used for residential and workplace applications with diluted NMP, which ranged from 25-53% concentration (i.e., 75-47% dilution).
73	Re-running residential exposures for MOEs	The internal dose estimates and MOEs have been recalculated with the updated PBPK models.

74	A peer reviewer suggested the assessment should more clearly explain the dermal absorption model and rate constants.	The PBPK model has dermal absorption of liquid and vapor NMP which both were fit to data from human exposure studies and the description of the PBPK dermal model was improved and presented in the PBPK Appendix I.
75	A peer reviewer suggested that it is unclear that PBPK model predictions are adequate for the dermal exposure route	The PBPK model has dermal absorption of liquid and vapor NMP which both were fit to data from human exposure studies and the model fits of the EPA/OPPT modified PBPK model are presented in the PBPK Appendix I. (See also, response to question #76.)
76	A peer reviewer stated they could not determine that the PBPK model performs adequately for dermal vapor and inhalation exposures	The model fits of the EPA/OPPT modified PBPK model are adequate for dermal vapor and inhalation exposures and are presented in the PBPK Appendix I. Data to fully characterize the extent to which normal clothing acts as a barrier to NMP dermal vapor absorption are not available, hence this is an uncertainty in the modeling that cannot be resolved. However it is discussed in the PBPK Appendix I and since the human model is calibrated against whole-body exposures, we believe that vapor absorption and uptake are appropriately characterized. The development and application of the internal dose metrics are described in the PBPK Appendix I and the human health assessment section 3.2.2.
77	The peer reviewers agreed with the choice of the AUC as the internal dose metric for fetal BW PODs.	The NMP AUC is the chosen dose metric for evaluating reduced fetal body weight which is the most sensitive, consistent effect in repeated dose studies. The uncertainty is selection of dose metrics is discussed further in section 4.3.3.
78	The peer reviewers supported the choice of BMD analysis with internal doses from the PBPK model rather than the external, administered concentrations.	When sufficient information was available BMD analysis was applied for calculation of PODs in rats. The PODs in rats were converted to internal doses with the PBPK model. In studies with sufficient similarities the exposures were combined across routes using internal doses to provide a more extensive characterization of the dose response curve. MOEs were calculated by comparing internal doses in rats and humans this allowed MOEs to be calculated for combined inhalation and dermal exposures in human exposure scenarios.

Risk Assessment

Charge Question 9-1: Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the acute inhalation risks to consumers of NMP-based products and to bystanders/non-users (e.g., children, women of childbearing age), including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HECs. Please comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the acute inhalation risks.

Charge Question 9-2: Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the chronic inhalation risks to workers using NMP-based products, including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HECs. Please also comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the chronic inhalation risks.

Charge Question 9-3: Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the acute dermal risks to consumers of NMP-based products, including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HEDs. Please also comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the acute dermal risks.

Charge Question 9-4: Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the chronic dermal risks to workers of NMP-based products, including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HEDs. Please also comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the chronic dermal risks.

Charge Question 9-4: Please comment on whether the risk assessment document has adequately described the uncertainties and data limitations in the methodology used to assess risks to allow the EPA to reduce risks to human health from NMP. Please comment on whether this information is presented in a transparent manner.

#	Summary of Peer Review and Public Comments for Specific Issues Related to Charge Questions 1-1 and 1-2	EPA/OPPT Response
79	A public commenter suggested that the Margins of Exposure (MOE) for occupational and residential exposure scenarios should be calculated by summing the MOE for the inhalation exposure and the MOE for the pooled exposures from all other relevant routes.	The MOEs for occupational and consumer scenarios are calculated for the combined inhalation and dermal exposures. The assessment was updated to include a description of how the MOEs are calculated in Section 1.2.4 Conceptual Model and shown in Figure 1-3.

80	A peer review panelist agreed that the MOE of 30 appears to be appropriate, but indicated that there has not been a comprehensive data gap analysis to determine whether substantial uncertainties exist in the database. For example and most relevant to the acute scenario, we have no data regarding acute irritation or CNS effects. The workplace literature on NMP may give some idea of whether it elicits an acute response and at what level. Laboratory animals cannot tell the investigator when they have a headache. The low odor threshold relative to the modeled concentrations suggest that applicators and residential bystanders will detect the NMP odor which in some individuals may trigger an irritation response. These considerations can be part of a data gap analysis.	The target MOE of 30 will be retained and the justification has been provided in section 4.1. EPA/OPPT agrees that there are uncertainties due to data gaps. There were no reports of adverse effects, such as headaches or neurotoxicity, following the intentional human exposures, reviewed in Appendix G. Laboratory animal studies identified effects that might be suggestive of neurotoxicity, however the data are limited. A discussion of this uncertainty was added to section 4.3.3.
81	A peer review panelist suggested that EPA/OPPT improve risk communication. Quantitative probabilistic characterization of variability or uncertainty is not necessary in every risk assessment and in the current case, given the range of exposure and modeling scenarios run, it is likely that a reasonable array of different risks have been presented. This includes different user behaviors and different levels of protection	The revised risk assessment now identifies which scenarios and behaviors create the greatest risks: For occupational scenarios, the variables that were associated with elevated risks include: 1. Longer duration of worker contact time(4 or more hours) 2. Not using appropriate gloves 3. Higher concentration of NMP in the product.

	(gloves on or off, respiratory protection or not). Presenting the results of MOE analyses on all these exposure and modeling options could result in a potentially confusing array of risks. Therefore, it will be important for EPA/OPPT to communicate these clearly and perhaps sort thru the results to highlight *1) what scenarios and behaviors create the greatest risk; 2) what may represent the most likely risks; 3) what are the greatest contributors to risk (e.g., inhalation vs. dermal vapor vs. dermal liquid contact).*	Dermal exposures without gloves produces the highest internal doses, hence drive risks and use of appropriate gloves will greatly reduce exposures in the occupational environment. Inhalation absorption is the second largest contributor to internal dose. Clearly this can be mitigated by use of a respirator and/or good ventilation. While dermal absorption of NMP vapor through the skin also contributes significantly, especially in the absence of liquid contact, the risks from this pathway alone are minimal.
82	Given the importance of dermal exposure, the lack of chronic toxicology studies by the dermal route represents a data gap but this may be considered minor relative to the availability of other types of dermal and inhalation testing.	Uncertainties regarding dermal exposure are addressed in 4.3.
83	Discussion of how assumptions, parameters, etc. lead to the under or over-estimation of risks USEPA/OPPT can consider an over/under approach in which best professional judgment is used to state whether a given uncertainty is likely a source of over-estimation, under-estimation or unclear (toxicology data gaps). This could help the reader understand whether overall, the assumptions and uncertainties tend to go in	EPA/OPPT incorporated a more detailed elucidation of the consequences of the assumptions used and decisions made and how they affect the risk assessment. See the “Key sources of Uncertainty and Data Limitations” section 4.3.

	one direction or the other. Another approach is to identify the risk drivers (e.g., time spent actually doing the stripping) and describing the range of values used vs. the range of all values possible and the uncertainty in the underlying data.	
84	Document did not fully address all of the uncertainties: a) Potential for the bystander exposure to be a young child, with attendant greater skin surface area, respiratory rate and slower NMP metabolism. b) Potential toxicological data gaps or uncertainties presented by the underlying data as described in preceding sections. For example, the acute neurotoxic potential of NMP is not discussed. Given the relatively high concentrations simulated, much higher than the NMP odor threshold, it is possible that there could be acute irritation and neurological effects. This possibility should be considered from the perspective of surveys and reports from the workplace and any other studies or clinical reports. c) The rationale for the extrapolation between gestational developmental data to acute exposure scenarios could be improved	a) In the final risk assessment, EPA included calculations based on a young child near to the consumer user. This was described in section 4.1. b) Revisions were made the uncertainties section, including a description of uncertainties associated with neurotoxicity. Also, although NMP is reported to be irritating, there were no reports of irritating effects in the intentional human studies, used for validating the PBPK model and described in appendix G. c) The revised risk assessment includes a more detailed description of the rationale for the use of developmental toxicity studies in the evaluation and selection of key endpoints for acute exposure scenarios (Section 3.1.3.4) and the van Raiij reference and others are cited. d) This comment is no longer applicable because contact/per day was not used in the harmonized approach to exposure assessment. e) EPA/OPPT has broadened the inhalation data used in the occupational exposure assessment and created two assessed populations in the assessment. These populations are expected to cover the entirety of categories of workers who may be exposed to NMP-based strippers and NMP-based graffiti remover products. Therefore, the use of the broader data negates the need to consider modeling of worker inhalation exposures.

	and the van Raiij reference is an excellent resource for this purpose. d) EPA/OPPT identifies one episode of dermal contact/day as an uncertainty. It would seem that the uncertainty of this assumption could be addressed in more depth. e) The air concentrations assumed for workers are based upon a limited amount of data for outdoor graffiti removal workers. These air estimates are considerably lower than the air estimates for the residential scenario, even the non-user. This discrepancy may be due to the indoor/outdoor exposure differences. However, there would appear to be many workers that would be handling NMP indoors. Thus, the use of graffiti workers as the occupational basis would present a rather large uncertainty and potential for underestimation.	
85	Uncertainties in the assumption of one exposure per day to the hands (both occupational and consumer exposure assessments)	The harmonized consumer and occupational assessments assume continuous exposure to NMP when working with the paint stripper. The occupational dermal exposure is assumed to be continuous for the duration of the work period (section 2.1.1.3). For consumer dermal exposure use patterns reported in the literature were used (section 2.2.1.1).
86	A peer review panelist suggested that the draft risk assessment contained misleading conclusions about risks to consumers.	The final risk assessment, which refined the exposure assessment by incorporating a PBPK model, and included a range of exposure durations, and product concentrations. The outcome of the risk assessment demonstrates

	Specifically, the conclusion on page 64 state that "Consumers may have potential risks of concern from inhalation exposure if exposed for more than 4 hours at lower ventilation rates." This is misleading because a) MOEs were not calculated for <4 hours inhalation exposure, so it should be made clear that this doesn't imply that shorter duration exposures are safe; and b) It's a bit ambiguous to say the risk is "at lower ventilation rates." The MOE for scenario 4 (spray application, central tendency scenario) was <30 and this was at the higher ventilation rate modeled. Scenario 2 also had an MOE <30 for the user and was at the higher ventilation rate. Furthermore, every scenario except 7 & 8 assumed open windows (relatively good ventilation), whereas there is evidence suggesting that a substantial proportion of users do not open the windows when using paint strippers (Riley 2001). So, the message should not be that risk occurs at lower ventilation rates, since that implies that risk is only at low ventilation rates.	that duration of use and product concentration are both important drivers of risk. Short term (*e.g.*, 1-2 hour) exposures to products with low concentrations of NMP (*e.g.*, 25% or less) result in no risks. However, the use of higher concentration products that can readily be purchased by both consumers and workers may result in risks. The risk assessment was revised throughout to more clearly explain a number of considerations, including that dermal exposure is the more important exposure route, and that use of appropriate gloves would significantly reduce dermal exposures and risks.
87	A peer review panelist noted that the potential for children to receive a higher dose due to increased surface area and respiratory rate per body weight, as well as the potential for slower metabolism of parent compound, has not been evaluated.	While a child's metabolic capacity is developing in the first months of life, the data we've reviewed indicate that it's at essentially adult levels (consistent with allometric scaling) by 1 year of age if not sooner. Simulations were run for a 9-kg, 75 cm tall person which is the approximate weight and height for a 1-year-old girl from the exposure factors handbook Air concentrations for the "rest of house" consumer scenarios were used as inputs. While children have

		faster respiration/BW and higher skin SA/BW, once they are metabolic competent that metabolism is also expected to be relatively faster based on allometric scaling. The resulting simulations predict that while peak concentrations in the child would be 22-34% higher than a 74 kg adult woman, the blood AUC would actually be 0.6 to 2.4% **lower** than the adult. While these simulations indicate only moderate variation in internal dose between children and adults, it must be kept in mind that the minimum MOE includes a factor of 10 for intra-human variability which is specifically intended to protect sensitive populations. It is generally assumed that this factor is a combination of a 3-fold factor for PK variability and 3-fold for PD. The simulations above indicate that absent reduced metabolic capability, children's internal doses are well within this 3-fold factor, hence it is unlikely that even the youngest infants would exceed that factor. Further, the simulations for rest-of-house residential exposures showed a MOE that well exceeded the benchmark MOE. In addition, the MOEs in this assessment are based on fetal endpoints. Toxicological endpoints that may be relevant to children (e.g., systemic effects) tend to occur in laboratory animals at higher doses. Considering that residential use is only expected to occur for a single day at a time and the large MOEs estimated for nonusers, the effect of this exposure on the developing child is not expected to be of concern. The greatest acute risk is to the fetus and impacts on growth would only be expected for more long-term exposures.
88	A public commenter suggested the use of the OSHA PEL to evaluate risks.	The Occupational Safety and Health Administration (OSHA) has not established regulatory exposure limits for NMP.

89	A public commenter questioned the decision to exclude acute exposure risk estimates for workers and occupational bystanders.	EPA/OPPT included in the final report the assessment of acute exposure risks for workers and nearby non-users.
90	Peer review panel members suggested that the uncertainties and data limitations discussion for worker exposures could be improved, particularly related to directional impact on risk and making the discussion more complete and robust. Also please add more consideration of uncertainties regarding glove use.	EPA/OPPT determined gaps in the discussion and completed improvements in section 4.3.1. The discussion was made more complete and robust, although directional impacts on risk could not be determined for any of the uncertainties so could not be included. Glove use information was also made more robust and included in Appendix D.

REFERENCES CITED

Abt Associates, I. 1992. *Methylene Chloride Consumer Products Use Survey Findings.* OMB #3041-0098. Prepared by Abt Associates, Inc. for the US Consumer Product Safety Commission, Bethesda, MD.

Anundi, H., S. Langworth, G. Johanson, M. L. Lind, B. Akesson, L. Friis, N. Itkes, E. Soderman, B. Jonsson, and C. Edling. 2000. *Air and Biological Monitoring of Solvent Exposure During Graffiti Removal*. International Archives of Occupational and Environmental Health, 73(8), 561-569.

Anundi, H., M. Lind, L. Friis, N. Itkes, S. Langworth, and C. Edling. 1993. *High Exposures to Organic Solvents among Graffiti Removers*. International Archives of Occupational and Environmental Health, 65(4), 247-251.

Becci, P., M. Knickerbocker, E. Reagan, R. Parent, and L. Burnette. 1982. *Teratogenicity Study of N-Methylpyrrolidone after Dermal Application to Sprague-Dawley Rats*. Fundamental and Applied Toxicology, 2(2), 73-76.

CDC. 2012a. *Fatal Exposure to Methylene Chloride among Bathtub Refinishers -- United States, 2000-2011*. Mobidity and Mortality Weekly Report, 61(7), 119-122.

CDC (Centers for Disease Control and Prevention). 2012b. *Tub Refinisher Died Due to Methylene Chloride Overexposure While Stripping a Bathtub. Michigan Case Report: 10m1013*. http://www.cdc.gov/niosh/face/stateface/mi/10MI013.html (accessed on August 1, 2012).

DuPont (EI du Pont de Nemours and Company,). 1990. *1-Methyl-2-Pyrrolidinone (NMP): Reproductive and Developmental Toxicity in the Rat*. HLR 294-90. Medical Research Project 3872-001/HLR 294-90, unpublished data, 05 Oct 1990.

EPA (US Environmental Protection Agency). 1991. *Guidelines for Developmental Toxicity Risk Assessment*. EPA/600/FR-91/001. Risk Assessment Forum, Washington, DC. http://www.epa.gov/raf/publications/pdfs/DEVTOX.pdf.

EPA (US Environmental Protection Agency). 1992. *Dermal Exposure Assessment: Principles and Applications (Interim Report)*. EPA/600/8-91/011B. Office of Health and Environmental Assessment, Washington, DC.

EPA (US Environmental Protection Agency). 1994. *Consumer Exposure to Paint Stripper Solvents*. EPA Contract No 68-DO-0137. MRI, Washington, DC.

EPA (US Environmental Protection Agency). 2011. *Exposure Factors Handbook: 2011 Edition*. National Center for Environmental Assessment, Washington, DC. http://www.epa.gov/ncea/efh/pdfs/efh-complete.pdf.

EPA (US Environmental Protection Agency). 2012. *Benchmark Dose Technical Guidance*. EPA/100/R-12/001. Risk Assessment Forum, Washington, DC. http://www.epa.gov/raf/publications/pdfs/benchmark_dose_guidance.pdf.

HSDB (National Library of Medicine). 2012. *Hazardous Substances Data Bank. 1-Methyl-2-Pyrrolidinone*. National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB (July 24, 2012).

Kavlock, R. J., B. C. Allen, E. M. Faustman, and C. A. Kimmel. 1995. *Dose-Response Assessments for Developmental Toxicity: IV. Benchmark Doses for Fetal Weight Changes*. Fundamental and Applied Toxicology, 26, 211-222.

Pollack-Nelson, C. 1995. *Analysis of Methylene Chloride Product Labelling*. Ergonomics, 38(11), 2176-2187.

Riley, D. M., B. Fischhoff, M. J. Small, and P. Fischbeck. 2001. *Evaluating the Effectiveness of Risk-Reduction Strategies for Consumer Chemical Products*. Risk Analysis, 21(2), 357-369.

Saillenfait, A. M., F. Gallissot, I. Langonne, and J. P. Sabate. 2002. *Developmental Toxicity of N-Methyl-2-Pyrrolidone Administered Orally to Rats*. Food Chemistry and Toxicology, 40(11), 1705-1712.

Saillenfait, A. M., F. Gallissot, and G. Morel. 2003. *Developmental Toxicity of N-Methyl-2-Pyrrolidone in Rats Following Inhalation Exposure*. Food Chemistry and Toxicology, 41(4), 583-588.

Solomon, G. M., E. P. Morse, M. J. Garbo, and D. K. Milton. 1996. *Stillbirth after Occupational Exposure to N-Methyl-2-Pyrrolidone. A Case Report and Review of the Literature*. Journal of Occupational and Environmental Medicine, 38(7), 705-713.

US EPA (US Environmental Protection Agency). 1994. Consumer exposure to paint stripper solvents, Washington, DC.

Van Raaij, M. T. M., A. H. Janssen, and A. H. Piersma. 2003. *The Relevance of Developmental Toxicity Endpoints for Acute Limit Setting* RIVM Report 601900004.