United States
Environmental Protection Agency

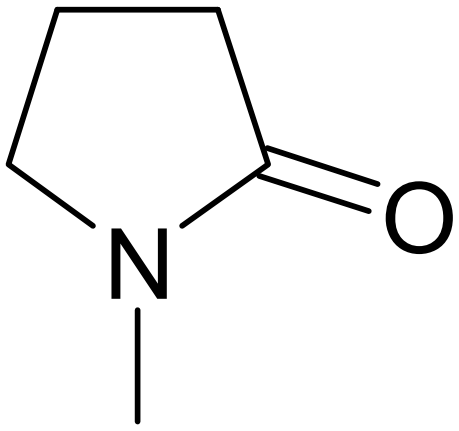
Office of Chemical Safety and
Pollution Prevention

Final Risk Evaluation for n-Methylpyrrolidone

Systematic Review Supplemental File:

Data Quality Evaluation of Human Health Hazard Studies - Epidemiological Studies

CASRN: 872-50-4



December 2020

Table Listing

This document presents data quality evaluation results for epidemiological studies evaluated for the NMP Risk Evaluation.

EPA's Office of Pollution Prevention and Toxics (OPPT) developed data quality criteria for epidemiological studies. The first version of the criteria was documented in the *Application of Systematic Review in TSCA Risk Evaluations* document (EPA Document #740-P1-8001). The initial criteria were updated as described in the supplemental file *Final Risk Evaluation for n-Methylpyrrolidone (NMP) Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies, Docket EPA-HQ-OPPT-2019-0236.*

Table 1: **Nishimura et al., 2009: Evaluation of Musculoskeletal/Motor Function Outcomes**

Study Citation:	Nishimura, S., Yasui, H., Miyauchi, H., Kikuchi, Y., Kondo, N., Takebayashi, T., Tanaka, S., Mikoshiba, Y., Omae, K., Nomiyama, T. (2009). A cross-sectional observation of effect of exposure to N-methyl-2-pyrrolidone (NMP) on workers' health Industrial Health, 47(4), 355-362
Data Type:	Cross-sectional_Occupational_NMP_MotorFunction_MCV_Mean-Musculoskeletal/Motor Function
HERO ID:	735269

Domain	Metric		Rating†	MWF*	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant Selection	Low	× 0.4	1.2	Participants include 15 male workers in a factory using NMP for cleaning instruments without protective respiratory devices or clothing (wore polyethylene gloves). Not stated if these 15 encompassed the entire exposed workforce or a select subset. No information provided on participation rate, inclusion or exclusion criteria, or methods of participation selection.
	Metric 2:	Attrition	High	× 0.4	0.4	One exposed worked excluded from study, because he missed work on the day of health effects exam.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls selected from workers at the same factory with no occupational NMP exposure, matched by age, education and work load. No significant differences in age, physical status, education, drinking levels or smoking habits. Controls were only sampled on the last day of the 5 day study, compared to daily sampling in exposed group.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Sampling tube of 400 mg activated charcoal and air sampling pump (flow rate 0.1 L /min) worn for 8 hr/ day for 1 week (exposed) or 1 day (controls). Analyzed with GC-MS. See reference (Xiafei 200) for details.
	Metric 5:	Exposure Levels	Low	× 0.2	0.6	Exposure maximum (0.80 ppm) and daily means (0.14-0.26 ppm) were below the OEL of 1 ppm recommended by the Japan Society for Occupational Health (JSOH). Likely to result in a bias towards the null.
	Metric 6:	Temporality	Low	× 0.4	1.2	Outcomes measured directly after a 1-5 days of exposure, but history of exposure not stated. Outcomes of skin irritation/headaches expected to fall within this window, but some neurobehavioral outcomes (depression, response time, and nerve conductivity) may fall outside of this exposure window.
Domain 3: Outcome Assessment						

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Study Citation: Nishimura, S., Yasui, H., Miyauchi, H., Kikuchi, Y., Kondo, N., Takebayashi, T., Tanaka, S., Mikoshiba, Y., Omae, K., Nomiyama, T. (2009). A cross-sectional observation of effect of exposure to N-methyl-2-pyrrolidone (NMP) on workers' health Industrial Health, 47(4), 355-362

Data Type: Cross-sectional_Occupational_NMP_MotorFunction_MCV_Mean-Musculoskeletal/Motor Function

HERO ID: 735269

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome Measurement or Characterization	Medium	× 0.667	1.33	Motor and sensory nerve conduction velocities of median nerve of dominant arm (Neuropack). Neurobehavioral tests (finger tapping, response time, reaction time, digit span, and Benton visual retention test) carried out on a personal computer. These objective metrics would be ranked high. Subjective symptoms (>50 subjective symptoms, depression, and anxiety) were determined from self-administered questionnaires, which would be ranked as low. Therefore, the full study was ranked as medium.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	States that no significant differences were reported in symptoms related to irritation, but no data provided. All other outcomes fully reported and extractable.
Domain 4: Potential Confounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Multiple regression, multiple logistic regression and stratification were used to adjust for potential confounders including age, education, BMI and smoking/drinking habits. These results were not quantitatively reported, however, the exposed and control groups do not have significant differences with regards to these covariates.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Smoking and medical histories collected from self-administered questionnaires. Source of age, body weight information not stated.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Identified co-exposure to xylene (10% of cleaning solution), which was measured by a NIOSH method. Primary xylene metabolite (methylhippuric acid) was measured in urine. Both measurements fell below the limits of detection (0.1 ppm in air and 0.01 mg/dL in urine).
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design is appropriate for the outcomes measured. Means, standard deviations and number of participants reported for outcomes. Linear regression conducted, but quantitative results not presented.

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Study Citation:	Nishimura, S., Yasui, H., Miyauchi, H., Kikuchi, Y., Kondo, N., Takebayashi, T., Tanaka, S., Mikoshiba, Y., Omae, K., Nomiyama, T. (2009). A cross-sectional observation of effect of exposure to N-methyl-2-pyrrolidone (NMP) on workers' health Industrial Health, 47(4), 355-362
Data Type:	Cross-sectional_Occupational_NMP_MotorFunction_MCV_Mean-Musculoskeletal/Motor Function
HERO ID:	735269

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
	Metric 13: Statistical Power	Medium	× 0.2	0.4	Number of participants (14 exposed, 15 controls) is small and no information on the derivation of statistical power is provided. The number of participants is assumed to be adequate.
	Metric 14: Reproducibility of Analyses	Medium	× 0.2	0.4	Simple analysis is reproducible.
	Metric 15: Statistical Models	Medium	× 0.2	0.4	Means with standard deviations presented for outcomes. Regression models not discussed in detail, but not reported either. The presented analysis is sufficient.
Domain 6: Other Considerations for Biomarker Selection and Measurement					
	Metric 16: Use of Biomarker of Exposure	Medium	× 0.167	0.33	NMP was used as a biomarker, not its metabolites. Previous study showed that it can be reflective of exposure (Bader 2007), but it was not a quantitative association in this study. All workers with inhalation exposure had NMP in urine, while all controls had NMP below the limit of detection.
	Metric 17: Effect Biomarker	Not Rated	NA	NA	Biomarker not used for effects.
	Metric 18: Method Sensitivity	Medium	× 0.167	0.33	LOD stated and sufficiently low to detect biomarker in all exposed samples.
	Metric 19: Biomarker Stability	Medium	× 0.167	0.33	Urine samples stored at 4C, which differs from the 80C stated in the method reference (Xiaofei 2000). Stability and time between collection and analysis not stated in either study.
	Metric 20: Sample Contamination	Medium	× 0.167	0.33	Aside from requesting that participants washed their hands before providing samples, no information is provided regarding contamination.
	Metric 21: Method Requirements	Medium	× 0.167	0.33	GC-MS used for high degree of confidence in chemical identification.
	Metric 22: Matrix Adjustment	High	× 0.167	0.17	Creatinine adjusted and unadjusted values provided (Table 2).
Overall Quality Determination[‡]		Medium		2.0	
Extracted		Yes			

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Study Citation:	Nishimura, S., Yasui, H., Miyauchi, H., Kikuchi, Y., Kondo, N., Takebayashi, T., Tanaka, S., Mikoshiba, Y., Omae, K., Nomiyama, T. (2009). A cross-sectional observation of effect of exposure to N-methyl-2-pyrrolidone (NMP) on workers' health Industrial Health, 47(4), 355-362
Data Type:	Cross-sectional_Occupational_NMP_MotorFunction_MCV_Mean-Musculoskeletal/Motor Function
HERO ID:	735269

Domain	Metric	Rating†	MWF⋆	Score	Comments††

⋆ MWF = Metric Weighting Factor
† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.
‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High: $\geq$ 1 to $<$ 1.7; Medium: $\geq$ 1.7 to $<$ 2.3; Low: $\geq$ 2.3 to $\leq$ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study.

Table 2: **Nishimura et al., 2009: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Nishimura, S., Yasui, H., Miyauchi, H., Kikuchi, Y., Kondo, N., Takebayashi, T., Tanaka, S., Mikoshiba, Y., Omae, K., Nomiyama, T. (2009). A cross-sectional observation of effect of exposure to N-methyl-2-pyrrolidone (NMP) on workers' health Industrial Health, 47(4), 355-362
Data Type:	Cross-sectional_Occupational_NMP_Neurological_BentonVisual_Mean-Neurological/Behavior
HERO ID:	735269

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant Selection	Low	× 0.4	1.2	Participants include 15 male workers in a factory using NMP for cleaning instruments without protective respiratory devices or clothing (wore polyethylene gloves). Not stated if these 15 encompassed the entire exposed workforce or a select subset. No information provided on participation rate, inclusion or exclusion criteria, or methods of participation selection.
	Metric 2: Attrition	High	× 0.4	0.4	One exposed worked excluded from study, because he missed work on the day of health effects exam.
	Metric 3: Comparison Group	High	× 0.2	0.2	Controls selected from workers at the same factory with no occupational NMP exposure, matched by age, education and work load. No significant differences in age, physical status, education, drinking levels or smoking habits. Controls were only sampled on the last day of the 5 day study, compared to daily sampling in exposed group.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	High	× 0.4	0.4	Sampling tube of 400 mg activated charcoal and air sampling pump (flow rate 0.1 L /min) worn f or 8 hr/day for 1 week (exposed) or 1 day (controls). An-alyzed with GC-MS. See reference (Xiafei 200) for details.
	Metric 5: Exposure Levels	Low	× 0.2	0.6	Exposure maximum (0.80 ppm) and daily means (0.14-0.26 ppm) were below the OEL of 1 ppm recommended by the Japan Society for Occupational Health (JSOH). Likely to result in a bias towards the null.
	Metric 6: Temporality	Low	× 0.4	1.2	Outcomes measured directly after a 1-5 days of exposure, but history of exposure not stated. Outcomes of skin irritation/headaches expected to fall within this window, but some neurobehavioral outcomes (depression, response time, and nerve conductivity) may fall outside of this exposure window.
Domain 3: Outcome Assessment					

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Study Citation: Nishimura, S., Yasui, H., Miyauchi, H., Kikuchi, Y., Kondo, N., Takebayashi, T., Tanaka, S., Mikoshiba, Y., Omae, K., Nomiyama, T. (2009). A cross-sectional observation of effect of exposure to N-methyl-2-pyrrolidone (NMP) on workers' health Industrial Health, 47(4), 355-362

Data Type: Cross-sectional_Occupational_NMP_Neurological_BentonVisual_Mean-Neurological/Behavior

HERO ID: 735269

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 7:	Outcome Measurement or Characterization	Medium	× 0.667	1.33	Motor and sensory nerve conduction velocities of median nerve of dominant arm (Neuropack). Neurobehavioral tests (finger tapping, response time, reaction time, digit span, and Benton visual retention test) carried out on a personal computer. These objective metrics would be ranked high. Subjective symptoms (>50 subjective symptoms, depression, and anxiety) were determined from self-administered questionnaires, which would be ranked as low. Therefore, the full study was ranked as medium.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	States that no significant differences were reported in symptoms related to irritation, but no data provided. All other outcomes fully reported and extractable.
Domain 4: Potential Confounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Multiple regression, multiple logistic regression and stratification were used to adjust for potential confounders including age, education, BMI and smoking/drinking habits. These results were not quantitatively reported, however, the exposed and control groups do not have significant differences with regards to these covariates.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Smoking and medical histories collected from self-administered questionnaires. Source of age, body weight information not stated.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Identified co-exposure to xylene (10% of cleaning solution), which was measured by a NIOSH method. Primary xylene metabolite (methylhippuric acid) was measured in urine. Both measurements fell below the limits of detection (0.1 ppm in air and 0.01 mg/dL in urine).
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design is appropriate for the outcomes measured. Means, standard deviations and number of participants reported for outcomes. Linear regression conducted, but quantitative results not presented.

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Study Citation:	Nishimura, S., Yasui, H., Miyauchi, H., Kikuchi, Y., Kondo, N., Takebayashi, T., Tanaka, S., Mikoshiba, Y., Omae, K., Nomiyama, T. (2009). A cross-sectional observation of effect of exposure to N-methyl-2-pyrrolidone (NMP) on workers' health Industrial Health, 47(4), 355-362
Data Type:	Cross-sectional_Occupational_NMP_Neurological_BentonVisual_Mean-Neurological/Behavior
HERO ID:	735269

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 13: Statistical Power	Medium	× 0.2	0.4	Number of participants (14 exposed, 15 controls) is small and no information on the derivation of statistical power is provided. The number of participants is assumed to be adequate.
	Metric 14: Reproducibility of Analyses	Medium	× 0.2	0.4	Simple analysis is reproducible.
	Metric 15: Statistical Models	Medium	× 0.2	0.4	Means with standard deviations presented for outcomes. Regression models not discussed in detail, but not reported either. The presented analysis is sufficient.
Domain 6: Other Considerations for Biomarker Selection and Measurement					
	Metric 16: Use of Biomarker of Exposure	Medium	× 0.167	0.33	NMP was used as a biomarker, not its metabolites. Previous study showed that it can be reflective of exposure (Bader 2007), but it was not a quantitative association in this study. All workers with inhalation exposure had NMP in urine, while all controls had NMP below the limit of detection.
	Metric 17: Effect Biomarker	Not Rated	NA	NA	Biomarker not used for effects.
	Metric 18: Method Sensitivity	Medium	× 0.167	0.33	LOD stated and sufficiently low to detect biomarker in all exposed samples.
	Metric 19: Biomarker Stability	Medium	× 0.167	0.33	Urine samples stored at 4C, which differs from the 80C stated in the method reference (Xiaofei 2000). Stability and time between collection and analysis not stated in either study.
	Metric 20: Sample Contamination	Medium	× 0.167	0.33	Aside from requesting that participants washed their hands before providing samples, no information is provided regarding contamination.
	Metric 21: Method Requirements	Medium	× 0.167	0.33	GC-MS used for high degree of confidence in chemical identification.
	Metric 22: Matrix Adjustment	High	× 0.167	0.17	Creatinine adjusted and unadjusted values provided (Table 2).
Overall Quality Determination‡		Medium		2.0	
Extracted		Yes			

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Study Citation:	Nishimura, S., Yasui, H., Miyauchi, H., Kikuchi, Y., Kondo, N., Takebayashi, T., Tanaka, S., Mikoshiba, Y., Omae, K., Nomiyama, T. (2009). A cross-sectional observation of effect of exposure to N-methyl-2-pyrrolidone (NMP) on workers' health Industrial Health, 47(4), 355-362
Data Type:	Cross-sectional_Occupational_NMP_Neurological_BentonVisual_Mean-Neurological/Behavior
HERO ID:	735269

Domain	Metric	Rating†	MWF⋆	Score	Comments††

⋆ MWF = Metric Weighting Factor
† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.
‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High: $\geq$ 1 to $<$ 1.7; Medium: $\geq$ 1.7 to $<$ 2.3; Low: $\geq$ 2.3 to $\leq$ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study.

Table 3: **Haufroid et al., 2014: Evaluation of Renal Outcomes**

Study Citation:	Haufroid, V; Jaeger, VK; Jeggli, S; Eisenegger, R; Bernard, A; Friedli, D; Lison, D; Hotz, P (2014). Biological monitoring and health effects of low-level exposure to N-methyl-2-pyrrolidone: a cross-sectional study International Archives of Occupational and Environmental Health, 87(6), 663-674
Data Type:	Cross-sectional_Occupational_NMP_Renalserumcreatinine_Median-Renal
HERO ID:	2654929

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant Selection	High	× 0.4	0.4	Occupational NMP study in Switzerland from 2006-2011. From an initial list of 61 potential companies, 21 were included in the final study. Exposures were related to graffiti removal or by solvent exposure (production or synthesis); not always daily exposures. Analysis conducted on 91 exposed workers and 114 unexposed workers (all males)
	Metric 2: Attrition	Medium	× 0.4	0.8	Of the 327 eligible workers, 207 (63%) participated. Exclusion based on desire of participants (113), organization reasons (7) and gender (1 woman). No indication of bias from non-participation.
	Metric 3: Comparison Group	High	× 0.2	0.2	Unexposed and exposed workers has similar distributions of age. Unexposed workers had a slightly higher education levels, were less likely to be smokers and had lower alcohol consumption. However, these differences were not large.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	Personal air sampling for a full day with solid sorbent tubes and pumps (150 ml/min); NMP determined with NIOSH method. Exposure noted to vary greatly by days, but samples only collected from one day. Monthly exposures estimated by occupational history.
	Metric 5: Exposure Levels	Low	× 0.2	0.6	Range of NMP: below LOD-25.8 mg/m3 (median 0.18 mg/m). Participants categorized into 5 groups based on current and past exposures: never exposed, former solvent exposure, current NMP exposure only, current solvent exposure (no NMP), current exposure to NMP and other solvents. Relatively low NMP exposure and use of protect equipment result in a limited ability to determine dose-response.

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Study Citation: Haufroid, V; Jaeger, VK; Jeggli, S; Eisenegger, R; Bernard, A; Friedli, D; Lison, D; Hotz, P (2014). Biological monitoring and health effects of low-level exposure to N-methyl-2-pyrrolidone: a cross-sectional study International Archives of Occupational and Environmental Health, 87(6), 663-674

Data Type: Cross-sectional_Occupational_NMP_Renalserumcreatinine_Median-Renal

HERO ID: 2654929

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Biomarkers for health outcomes measured directly after shift with air monitoring and again before next shift (16 hrs off of work). Clinical symptoms, such as skin irritation/headaches, determined within a week of air monitoring; only 37 workers (43% of "exposed" group) worked with NMP the day before clinical assessments. Biomarkers for liver, renal and respiratory health also expected to fall within this exposure window.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome Measurement or Characterization	Medium	× 0.667	1.33	Clinical outcomes (skin irritation, headaches, neurotoxic outcomes) assessed with a semi-structured clinical examination and questionnaires. Spirometry results assessed by 2 physicians. Biomarkers for haematological, renal, liver and respiratory health also used (see metrics 16-22).
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Clinical outcomes are briefly qualitatively described, and thus cannot be extracted. The outcome biomarkers are fully reported.
Domain 4: Potential Confounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	Adjustment for age, smoking (pack years & number of years since smoking cessation), skin disease, glove usage, and genetic factors considered in various analyses. Differences in nationality between exposed and controls were not provided, but most non-Swiss participants were German or Italian. Data on education provided, but not adjustment for this factor or SES. However, it is unclear if these covariates were considered in the analysis between NMP exposure and health outcomes.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Smoking status/history determined with questionnaire. Other covariates assumed to be collected from employment records, but this is not explicitly states.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Categorized based on exposure to additional organic solvents. Hand washing with organic solvents also noted on the day of biomonitoring data collection.
Domain 5: Analysis						

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Study Citation:	Haufroid, V; Jaeger, VK; Jeggli, S; Eisenegger, R; Bernard, A; Friedli, D; Lison, D; Hotz, P (2014). Biological monitoring and health effects of low-level exposure to N-methyl-2-pyrrolidone: a cross-sectional study International Archives of Occupational and Environmental Health, 87(6), 663-674
Data Type:	Cross-sectional_Occupational_NMP_Renalserumcreatinine_Median-Renal
HERO ID:	2654929

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research questions however the scarce data on symptomatic effects limited the analysis. Due to wide variation in daily NMP exposure for individual participants, only 43% of "exposed" workers worked with NMP the day before clinical examination. So determination of acute health effects in this population is somewhat compromised.
	Metric 13:	Statistical Power	Medium	× 0.2	0.4	Only 8 participants had exposure to only NMP, while 38 had current exposure a mix of organic solvents (including NMP), and 30 were never exposed to NMP or organic solvents. Although power calculations were done apriori, the number of symptomatic cases was low making interpretation difficult.
	Metric 14:	Reproducibility of Analyses	Medium	× 0.2	0.4	Description of analysis sufficient to understand and reproduce.
	Metric 15:	Statistical Models	Medium	× 0.2	0.4	Multiple linear regression models used for exposed group and for the entire group for 2-HSMI/5-HNMP and s-creatinine.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.143	0.14	2-HMSI (mg/l; before next shift) covered 70% of variance. Metabolites measured in urine have long half-lives (6-26 hrs) and are unique to NMP.
	Metric 17:	Effect Biomarker	Medium	× 0.143	0.29	Biomarkers for renal health (urinary RBP, urinary albumin, and serum creatinine), hepatic health (GGT expression), and respiratory health (serum CC16) were used. Well established, but mechanisms of action not described.
	Metric 18:	Method Sensitivity	Medium	× 0.143	0.29	Metabolites measured with LC-MS/MS and a LOQ of 0.2 mg/L.
	Metric 19:	Biomarker Stability	Medium	× 0.143	0.29	Storage history not described, but do not have a high likelihood of biomarker instability.
	Metric 20:	Sample Contamination	Low	× 0.143	0.43	Blanks used for NMP metabolites, but no documentation of steps used to ensure contamination free from collection to measurement.
	Metric 21:	Method Requirements	High	× 0.143	0.14	LC-MS/MS used for NMP metabolites
	Metric 22:	Matrix Adjustment	High	× 0.143	0.14	Creatinine adjusted and unadjusted values provided (Table 2).

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Study Citation:	Haufroid, V; Jaeger, VK; Jeggli, S; Eisenegger, R; Bernard, A; Friedli, D; Lison, D; Hotz, P (2014). Biological monitoring and health effects of low-level exposure to N-methyl-2-pyrrolidone: a cross-sectional study International Archives of Occupational and Environmental Health, 87(6), 663-674
Data Type:	Cross-sectional_Occupational_NMP_Renalserumcreatinine_Median-Renal
HERO ID:	2654929

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Overall Quality Determination‡		~~Medium~~ ⟶ Low§		~~2.0~~	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High: $\geq$ 1 to $<$ 1.7; Medium: $\geq$ 1.7 to $<$ 2.3; Low: $\geq$ 2.3 to $\leq$ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study.

§ Evaluator's explanation for rating change: "The effect outcome being reported is based on a very small number of exposed workers and the authors do not that the small number makes interpretation difficult."

Table 4: **Haufroid et al., 2014: Evaluation of Respiratory Outcomes**

Study Citation:	Haufroid, V; Jaeger, VK; Jeggli, S; Eisenegger, R; Bernard, A; Friedli, D; Lison, D; Hotz, P (2014). Biological monitoring and health effects of low-level exposure to N-methyl-2-pyrrolidone: a cross-sectional study International Archives of Occupational and Environmental Health, 87(6), 663-674
Data Type:	Cross-sectional_Occupational_NMP_LungCapacity_FEV1_Median-Respiratory
HERO ID:	2654929

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant Selection	High	× 0.4	0.4	Occupational NMP study in Switzerland from 2006-2011. From an initial list of 61 potential companies, 21 were included in the final study. Exposures were related to graffiti removal or by solvent exposure (production or synthesis); not always daily exposures. Analysis conducted on 91 exposed workers and 114 unexposed workers (all males)
	Metric 2: Attrition	Medium	× 0.4	0.8	Of the 327 eligible workers, 207 (63%) participated. Exclusion based on desire of participants (113), organization reasons (7) and gender (1 woman). No indication of bias from non-participation.
	Metric 3: Comparison Group	High	× 0.2	0.2	Unexposed and exposed workers has similar distributions of age. Unexposed workers had a slightly higher education levels, were less likely to be smokers and had lower alcohol consumption. However, these differences were not large.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	Personal air sampling for a full day with solid sorbent tubes and pumps (150 ml/min); NMP determined with NIOSH method. Exposure noted to vary greatly by days, but samples only collected from one day. Monthly exposures estimated by occupational history.
	Metric 5: Exposure Levels	Low	× 0.2	0.6	Range of NMP: below LOD-25.8 mg/m3 (median 0.18 mg/m). Participants categorized into 5 groups based on current and past exposures: never exposed, former solvent exposure, current NMP exposure only, current solvent exposure (no NMP), current exposure to NMP and other solvents. Relatively low NMP exposure and use of protect equipment result in a limited ability to determine dose-response.

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Study Citation:	Haufroid, V; Jaeger, VK; Jeggli, S; Eisenegger, R; Bernard, A; Friedli, D; Lison, D; Hotz, P (2014). Biological monitoring and health effects of low-level exposure to N-methyl-2-pyrrolidone: a cross-sectional study International Archives of Occupational and Environmental Health, 87(6), 663-674
Data Type:	Cross-sectional_Occupational_NMP_LungCapacity_FEV1_Median-Respiratory
HERO ID:	2654929

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Biomarkers for health outcomes measured directly after shift with air monitoring and again before next shift (16 hrs off of work). Clinical symptoms, such as skin irritation/headaches, determined within a week of air monitoring; only 37 workers (43% of "exposed" group) worked with NMP the day before clinical assessments. Biomarkers for liver, renal and respiratory health also expected to fall within this exposure window.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome Measurement or Characterization	Medium	× 0.667	1.33	Clinical outcomes (skin irritation, headaches, neurotoxic outcomes) assessed with a semi-structured clinical examination and questionnaires. Spirometry results assessed by 2 physicians. Biomarkers for haematological, renal, liver and respiratory health also used (see metrics 16-22).
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Clinical outcomes are briefly qualitatively described, and thus cannot be extracted. The outcome biomarkers are fully reported.
Domain 4: Potential Confounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	Adjustment for age, smoking (pack years & number of years since smoking cessation), skin disease, glove usage, and genetic factors considered in various analyses. Differences in nationality between exposed and controls were not provided, but most non-Swiss participants were German or Italian. Data on education provided, but not adjustment for this factor or SES. However, it is unclear if these covariates were considered in the analysis between NMP exposure and health outcomes.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Smoking status/history determined with questionnaire. Other covariates assumed to be collected from employment records, but this is not explicitly states.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Categorized based on exposure to additional organic solvents. Hand washing with organic solvents also noted on the day of biomonitoring data collection.
Domain 5: Analysis						

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Study Citation:	Haufroid, V; Jaeger, VK; Jeggli, S; Eisenegger, R; Bernard, A; Friedli, D; Lison, D; Hotz, P (2014). Biological monitoring and health effects of low-level exposure to N-methyl-2-pyrrolidone: a cross-sectional study International Archives of Occupational and Environmental Health, 87(6), 663-674
Data Type:	Cross-sectional_Occupational_NMP_LungCapacity_FEV1_Median-Respiratory
HERO ID:	2654929

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research questions however the scarce data on symptomatic effects limited the analysis. Due to wide variation in daily NMP exposure for individual participants, only 43% of "exposed" workers worked with NMP the day before clinical examination, so determination of acute health effects in this population is somewhat compromised.
	Metric 13:	Statistical Power	Medium	× 0.2	0.4	Only 8 participants had exposure to only NMP, while 38 had current exposure a mix of organic solvents (including NMP). For reported outcomes, and 30 were never exposed to NMP or organic solvents. Although power calculations were done apriori, the number of symptomatic cases was low making interpretation difficult.
	Metric 14:	Reproducibility of Analyses	Medium	× 0.2	0.4	Description of analysis sufficient to understand and reproduce.
	Metric 15:	Statistical Models	Low	× 0.2	0.6	Multiple linear regression models used for exposed group and for the entire group for some outcome but not FEV1.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.143	0.14	2-HMSI (mg/l; before next shift) covered 70% of variance. Metabolites measured in urine have long half-lives (6-26 hrs) and are unique to NMP.
	Metric 17:	Effect Biomarker	Medium	× 0.143	0.29	Biomarkers for renal health (urinary RBP, urinary albumin, and serum creatinine), hepatic health (GGT expression), and respiratory health (serum CC16) were used. Well established, but mechanisms of action not described.
	Metric 18:	Method Sensitivity	Medium	× 0.143	0.29	Metabolites measured with LC-MS/MS and a LOQ of 0.2 mg/L.
	Metric 19:	Biomarker Stability	Medium	× 0.143	0.29	Storage history not described, but do not have a high likelihood of biomarker instability.
	Metric 20:	Sample Contamination	Low	× 0.143	0.43	Blanks used for NMP metabolites, but no documentation of steps used to ensure contamination free from collection to measurement.
	Metric 21:	Method Requirements	High	× 0.143	0.14	LC-MS/MS used for NMP metabolites
	Metric 22:	Matrix Adjustment	High	× 0.143	0.14	Creatinine adjusted and unadjusted values provided (Table 2).

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Study Citation:	Haufroid, V; Jaeger, VK; Jeggli, S; Eisenegger, R; Bernard, A; Friedli, D; Lison, D; Hotz, P (2014). Biological monitoring and health effects of low-level exposure to N-methyl-2-pyrrolidone: a cross-sectional study International Archives of Occupational and Environmental Health, 87(6), 663-674
Data Type:	Cross-sectional_Occupational_NMP_LungCapacity_FEV1_Median-Respiratory
HERO ID:	2654929

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Overall Quality Determination‡		~~Medium~~ ⟶ Low§		~~2.0~~	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High: $\geq$ 1 to $<$ 1.7; Medium: $\geq$ 1.7 to $<$ 2.3; Low: $\geq$ 2.3 to $\leq$ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study.

§ Evaluator's explanation for rating change: "Effect based on a very small number of workers."

Table 5: **Haufroid et al., 2014: Evaluation of Hepatic Outcomes**

Study Citation:	Haufroid, V; Jaeger, VK; Jeggli, S; Eisenegger, R; Bernard, A; Friedli, D; Lison, D; Hotz, P (2014). Biological monitoring and health effects of low-level exposure to N-methyl-2-pyrrolidone: a cross-sectional study International Archives of Occupational and Environmental Health, 87(6), 663-674
Data Type:	Cross-sectional_Occupational_NMP_Liver_GGTlevels_Median-Hepatic
HERO ID:	2654929

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant Selection	High	× 0.4	0.4	Occupational NMP study in Switzerland from 2006-2011. From an initial list of 61 potential companies, 21 were included in the final study. Exposures were related to graffiti removal or by solvent exposure (production or synthesis); not always daily exposures. Analysis conducted on 91 exposed workers and 114 unexposed workers (all males)
	Metric 2: Attrition	Medium	× 0.4	0.8	Of the 327 eligible workers, 207 (63%) participated. Exclusion based on desire of participants (113), organization reasons (7) and gender (1 woman). No indication of bias from non-participation.
	Metric 3: Comparison Group	High	× 0.2	0.2	Unexposed and exposed workers has similar distributions of age. Unexposed workers had a slightly higher education levels, were less likely to be smokers and had lower alcohol consumption. However, these differences were not large.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	Personal air sampling for a full day with solid sorbent tubes and pumps (150 ml/min); NMP determined with NIOSH method. Exposure noted to vary greatly by days, but samples only collected from one day. Monthly exposures estimated by occupational history.
	Metric 5: Exposure Levels	Low	× 0.2	0.6	Range of NMP: below LOD-25.8 mg/m3 (median 0.18 mg/m). Participants categorized into 5 groups based on current and past exposures: never exposed, former solvent exposure, current NMP exposure only, current solvent exposure (no NMP), current exposure to NMP and other solvents. Relatively low NMP exposure and use of protect equipment result in a limited ability to determine dose-response.

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Study Citation:	Haufroid, V; Jaeger, VK; Jeggli, S; Eisenegger, R; Bernard, A; Friedli, D; Lison, D; Hotz, P (2014). Biological monitoring and health effects of low-level exposure to N-methyl-2-pyrrolidone: a cross-sectional study International Archives of Occupational and Environmental Health, 87(6), 663-674
Data Type:	Cross-sectional_Occupational_NMP_Liver_GGTlevels_Median-Hepatic
HERO ID:	2654929

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Biomarkers for health outcomes measured directly after shift with air monitoring and again before next shift (16 hrs off of work). Clinical symptoms, such as skin irritation/headaches, determined within a week of air monitoring; only 37 workers (43% of "exposed" group) worked with NMP the day before clinical assessments. Biomarkers for liver, renal and respiratory health also expected to fall within this exposure window.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome Measurement or Characterization	Medium	× 0.667	1.33	Clinical outcomes (skin irritation, headaches, neurotoxic outcomes) assessed with a semi-structured clinical examination and questionnaires. Spirometry results assessed by 2 physicians. Biomarkers for haematological, renal, liver and respiratory health also used (see metrics 16-22).
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Clinical outcomes are briefly qualitatively described, and thus cannot be extracted. The outcome biomarkers are fully reported.
Domain 4: Potential Confounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	Adjustment for age, smoking (pack years & number of years since smoking cessation), skin disease, glove usage, and genetic factors considered in various analyses. Differences in nationality between exposed and controls were not provided, but most non-Swiss participants were German or Italian. Data on education provided, but not adjustment for this factor or SES. However, it is unclear if these covariates were considered in the analysis between NMP exposure and health outcomes.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Smoking status/history determined with questionnaire. Other covariates assumed to be collected from employment records, but this is not explicitly states.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Categorized based on exposure to additional organic solvents. Hand washing with organic solvents also noted on the day of biomonitoring data collection.
Domain 5: Analysis						

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Study Citation:	Haufroid, V; Jaeger, VK; Jeggli, S; Eisenegger, R; Bernard, A; Friedli, D; Lison, D; Hotz, P (2014). Biological monitoring and health effects of low-level exposure to N-methyl-2-pyrrolidone: a cross-sectional study International Archives of Occupational and Environmental Health, 87(6), 663-674
Data Type:	Cross-sectional_Occupational_NMP_Liver_GGTlevels_Median-Hepatic
HERO ID:	2654929

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research questions however the scarce data on symptomatic effects limited the analysis. Due to wide variation in daily NMP exposure for individual participants, only 43% of "exposed" workers worked with NMP the day before clinical examination, so determination of acute health effects in this population is somewhat compromised.
	Metric 13:	Statistical Power	Medium	× 0.2	0.4	Only 8 participants had exposure to only NMP, while 38 had current exposure a mix of organic solvents (including NMP). For reported outcomes, and 30 were never exposed to NMP or organic solvents. Although power calculations were done apriori, the number of symptomatic cases was low making interpretation difficult.
	Metric 14:	Reproducibility of Analyses	Medium	× 0.2	0.4	Description of analysis sufficient to understand and reproduce.
	Metric 15:	Statistical Models	Medium	× 0.2	0.4	Multiple linear regression models used for exposed group and for the entire group for 2-HSMI/5-HNMP and GGT.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.143	0.14	2-HMSI (mg/l; before next shift) covered 70% of variance. Metabolites measured in urine have long half-lives (6-26 hrs) and are unique to NMP.
	Metric 17:	Effect Biomarker	Medium	× 0.143	0.29	Biomarkers for renal health (urinary RBP, urinary albumin, and serum creatinine), hepatic health (GGT expression), and respiratory health (serum CC16) were used. Well established, but mechanisms of action not described.
	Metric 18:	Method Sensitivity	Medium	× 0.143	0.29	Metabolites measured with LC-MS/MS and a LOQ of 0.2 mg/L.
	Metric 19:	Biomarker Stability	Medium	× 0.143	0.29	Storage history not described, but do not have a high likelihood of biomarker instability.
	Metric 20:	Sample Contamination	Low	× 0.143	0.43	Blanks used for NMP metabolites, but no documentation of steps used to ensure contamination free from collection to measurement.
	Metric 21:	Method Requirements	High	× 0.143	0.14	LC-MS/MS used for NMP metabolites
	Metric 22:	Matrix Adjustment	High	× 0.143	0.14	Creatinine adjusted and unadjusted values provided (Table 2).

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Study Citation:	Haufroid, V; Jaeger, VK; Jeggli, S; Eisenegger, R; Bernard, A; Friedli, D; Lison, D; Hotz, P (2014). Biological monitoring and health effects of low-level exposure to N-methyl-2-pyrrolidone: a cross-sectional study International Archives of Occupational and Environmental Health, 87(6), 663-674
Data Type:	Cross-sectional_Occupational_NMP_Liver_GGTlevels_Median-Hepatic
HERO ID:	2654929

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Overall Quality Determination‡		Medium		2.0	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High: $\geq$ 1 to $<$ 1.7; Medium: $\geq$ 1.7 to $<$ 2.3; Low: $\geq$ 2.3 to $\leq$ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study.

Table 6: **Bader et al., 2006: Evaluation of Irritation Outcomes**

Study Citation:	Bader, M; Rosenberger, W; Rebe, T; Keener, SA; Brock, TH; Hemmerling, HJ; Wrbitzky, R (2006). Ambient monitoring and biomonitoring of workers exposed to N-methyl-2-pyrrolidone in an industrial facility International Archives of Occupational and Environmental Health, 79(5), 357-364
Data Type:	Cross-sectional_Occupational_NMP_Irritation-Irritation
HERO ID:	3539720

Domain	Metric	Rating†	MWF*	Score	Comments††
Domain 1: Study Participation					
Metric 1:	Participant Selection	Low	× 0.4	1.2	Participant selection not clear. 7 workers and 3 on-site examiners running the study in adhesive bonding facility in Germany volunteered to physical exams, interviews and urine samples before/after shifts. Number of eligible workers not stated.
Metric 2:	Attrition	Low	× 0.4	1.2	Participation rates at study stages and inclusion/exclusion criteria not stated.
Metric 3:	Comparison Group	Medium	× 0.2	0.4	Workers served as own controls (pre/post shift) for acute outcomes following a day of work after an exposure-free weekend. Personal exposures 0.9-15.5 mg/m3 across workers, with duties including foreman, maintenance, and production worker. Additionally, the 3 examiners conducting the study (physician, study coordinator, and technician) were exposed only to air contamination and included in analysis. Note that for at least 1 worker, the "pre-shift" sample/interview occurred 2 hours after their shift began. Characteristics not reported.
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Well established and detailed methods of direct exposure measurements. Ambient air monitoring of average workplace concentrations and short-term peaks monitored by stationary and personal air monitoring. NMP and metabolites (5-HNMP, 2-HMSI) measured in spot urine tests. Dermal exposure noted to occur (inconsistent PPE usage), but should be accounted for in the biomonitoring data.
Metric 5:	Exposure Levels	Low	× 0.2	0.6	Exposure range in workers ranged from < LOD to 472 ug/g while exposure in examiners ranged from < LOD to 123. The range and distribution are limited.

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Study Citation:	Bader, M; Rosenberger, W; Rebe, T; Keener, SA; Brock, TH; Hemmerling, HJ; Wrbitzky, R (2006). Ambient monitoring and biomonitoring of workers exposed to N-methyl-2-pyrrolidone in an industrial facility International Archives of Occupational and Environmental Health, 79(5), 357-364
Data Type:	Cross-sectional_Occupational_NMP_Irritation-Irritation
HERO ID:	3539720

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality established for post-shift measurements, but not for the pre-shift measurements. Two pre-shift urine sample contained NMP and metabolites. For worker 7 (pre-shift urine had NMP), the pre-shift sample was taken 2 hours AFTER the shift began. When considering these measurements served as controls, it is problematic.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome Measurement or Characterization	Medium	× 0.667	1.33	Examined before and after shifts by occupational physician for irritation of the eyes, mucus membranes and skin. Interviewed for related health effects. Bias is possible from both parties, due to awareness of exposure, but no direct evidence of misclassification. Presumably, the physician interviewed/examined themselves, as a subject in the study.
	Metric 8:	Reporting Bias	Low	× 0.333	1.0	Interview/examination results presented qualitatively for selected participants. Outcomes stated for "workers" and not directly linked to participant exposure or biomonitoring data.
Domain 4: Potential Confounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.667	2	Workplace and tasks presented (vary across 7 workers and 3 examiners), but no other characteristics (age, sex. . .). Comparison of pre-shift and post-shift outcomes mediates the concern here though.
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	No covariates/confounders were assessed.
	Metric 11:	Co-exposure Confounding	Low	× 0.333	1	Solvents used in cleaning process - aromatic hydrocarbons, acetone, propylene glycol monomethyl ether, and 3-methoxybutyl acetate. Residues in production vessels - glutaric and succinic acid dimethyl ester. Only low levels of acetone and aromatic hydrocarbons detected in air during cleaning procedures, thus co-exposures deemed negligible. Due to lapses in PPE, the glutaric and succinic acid dimethyl ester could still be relevant and weren't accounted for.
Domain 5: Analysis						

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Study Citation:	Bader, M; Rosenberger, W; Rebe, T; Keener, SA; Brock, TH; Hemmerling, HJ; Wrbitzky, R (2006). Ambient monitoring and biomonitoring of workers exposed to N-methyl-2-pyrrolidone in an industrial facility International Archives of Occupational and Environmental Health, 79(5), 357-364
Data Type:	Cross-sectional_Occupational_NMP_Irritation-Irritation
HERO ID:	3539720

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Unacceptable	× 0.143	0.02	Study design appropriate for monitoring acute exposure outcomes. Descriptive outcome reporting did not include any statistical methods (no means, medians. . .). Workers with common colds were not excluded.
	Metric 13:	Statistical Power	Unacceptable	× 0.071	0.01	Low statistical power (7 subjects, 3 controls, with varied levels of exposure). Unable to determine if effects related to exposure.
	Metric 14:	Reproducibility of Analyses	Medium	× 0.071	0.14	Sufficient detail reported for only statistical method applied (linear regression of air monitoring and post-shift biomonitoring). No statistical method applied to health outcomes.
	Metric 15:	Statistical Models	Low	× 0.071	0.21	No models used to calculate risk estimates. Linear regression personal air monitoring results and post-shift biomonitoring data (metabolite 5-HNMP in urine) appropriate and transparent.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.167	0.17	NMP and metabolites (5-HNMP, 2-HMSI) measured in spot urine tests. Shown by linear regression to correlate with ambient air exposure, and suspected to also account for dermal exposure.
	Metric 17:	Effect Biomarker	Not Rated	NA	NA	No biomarker of effect was measured.
	Metric 18:	Method Sensitivity	Medium	× 0.167	0.33	LOD reported and sufficiently low to detect parent and metabolites in 100%-40% of samples.
	Metric 19:	Biomarker Stability	Medium	× 0.167	0.33	Storage duration and stability not noted. Stored at 4C during study, and -27C in the laboratory.
	Metric 20:	Sample Contamination	Low	× 0.167	0.5	Blanks used for NMP metabolites, but no documentation of steps used to ensure contamination free from collection to measurement.
	Metric 21:	Method Requirements	Medium	× 0.167	0.33	Analyzed with GC-MS.
	Metric 22:	Matrix Adjustment	Medium	× 0.167	0.33	Only creatine-adjusted levels provided.
Overall Quality Determination‡			Unacceptable⋆⋆		2.4	
Extracted			No			

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Study Citation:	Bader, M; Rosenberger, W; Rebe, T; Keener, SA; Brock, TH; Hemmerling, HJ; Wrbitzky, R (2006). Ambient monitoring and biomonitoring of workers exposed to N-methyl-2-pyrrolidone in an industrial facility International Archives of Occupational and Environmental Health, 79(5), 357-364
Data Type:	Cross-sectional_Occupational_NMP_Irritation-Irritation
HERO ID:	3539720

Domain	Metric	Rating†	MWF⋆	Score	Comments††

** Consistent with our *Application of Systematic Review in TSCA Risk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, one or more of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is unacceptable} \\ \left\lfloor \sum_i \left(\text{Metric Score}_i \times \text{MWF}_i\right) / \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High: ≥ 1 to < 1.7; Medium: ≥ 1.7 to < 2.3; Low: ≥ 2.3 to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study.