United States
Environmental Protection Agency

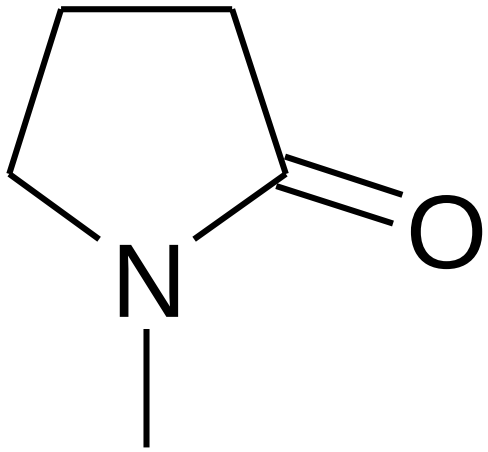
Office of Chemical Safety and
Pollution Prevention

Draft Risk Evaluation for N-Methylpyrrolidone

Systematic Review Supplemental File:

Data Quality Evaluation of Epidemiologic Studies

CASRN 872-50-4



October 2019

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Epidemiological Studies

1.1. Epidemiological evaluation results of the Bader et al 2006 study for irritation outcomes in general

Study reference:	**Bader, M.,Rosenberger, W.,Rebe, T.,Keener, S. A.,Brock, T. H.,Hemmerling, H. J.,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** **HERO ID: 3539720**					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	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.	Low	3	0.400	1.200
	2. Attrition	Participation rates at study stages and inclusion/exclusion criteria not stated.	Low	3	0.400	1.200
	3. Comparison Group	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.	Medium	2	0.200	0.400
Exposure Characterization	4. Measurement of Exposure	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.	High	1	0.400	0.400
	5. Exposure levels	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.	Low	3	0.200	0.600
	6. Temporality	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.	Medium	2	0.400	0.800

N-Methyl-2-pyrrolidone

Study reference:	Bader, M.,Rosenberger, W.,Rebe, T.,Keener, S. A.,Brock, T. H.,Hemmerling, H. J.,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 HERO ID: 3539720					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	7. Outcome measurement or characterization	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.	Medium	2	0.670	1.333
	8. Reporting Bias	Interview/examination results presented qualitatively for selected participants. Outcomes stated for "workers" and not directly linked to participant exposure or biomonitoring data.	Low	3	0.330	1.000
Potential Counfounding/Variable Control	9. Covariate Adjustment	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.	Low	3	0.670	2.000
	10. Covariate Characterization	No covariates/confounders were assessed.	Not Rated	NA	NA	NA
	11. Co-exposure Confounding	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.	Low	3	0.330	1.000
Analysis	12. Study Design and Methods	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.	Unacceptable	NA	NA	NA
	13. Statistical power	Low statistical power (7 subjects, 3 controls, with varied levels of exposure). Unable to determine if effects related to exposure.	Unacceptable	NA	NA	NA

N-Methyl-2-pyrrolidone

Study reference:	Bader, M.,Rosenberger, W.,Rebe, T.,Keener, S. A.,Brock, T. H.,Hemmerling, H. J.,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 HERO ID: 3539720					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	14. Reproducibility of analyses	Sufficient detail reported for only statistical method applied (linear regression of air monitoring and post-shift biomonitoring). No statistical method applied to health outcomes.	Medium	2	0.070	0.143
	15. Statistical models	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.	Low	3	0.070	0.214
Other	16. Use of Biomarker of Exposure	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.	High	1	0.170	0.167
	17. Effect biomarker	No biomarker of effect was measured.	Not Rated	NA	NA	NA
	18. Method Sensitivity	LOD reported and sufficiently low to detect parent and metabolites in 100%-40% of samples.	Medium	2	0.170	0.333
Confounding / Variable Control	19. Biomarker stability	Storage duration and stability not noted. Stored at 4C during study, and -27C in the laboratory.	Medium	2	0.170	0.333
	20. Sample contamination	Blanks used for NMP metabolites, but no documentation of steps used to ensure contamination free from collection to measurement.	Low	3	0.170	0.500
Data Presentation and Analysis	21. Method requirements	Analyzed with GC-MS.	Medium	2	0.170	0.333

N-Methyl-2-pyrrolidone

Study reference:	**Bader, M.,Rosenberger, W.,Rebe, T.,Keener, S. A.,Brock, T. H.,Hemmerling, H. J.,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** **HERO ID: 3539720**					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Matrix adjustment	Only creatine-adjusted levels provided.	Medium	2	0.170	0.333
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**5.14**	**12.3**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**2.945**	**Overall Score: Nearest *:**	**2.9[1]**
		Overall Quality Level:		**Unacceptable[1]**		
Study Quality Comment:	**The reviewer agreed with this study's overall quality level. Footnote 1: Consistent with our Application of A 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, two of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.**					

1.2. Epidemiological evaluation results of the Haufroid et al 2014 study for renal outcomes for cross-sectional occupational renal

Study reference:	**Haufroid, V.,Jaeger, V. K.,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** **HERO ID: 2654929**					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	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)	High	1	0.400	0.400
	2. Attrition	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.	Medium	2	0.400	0.800
	3. Comparison Group	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.	High	1	0.200	0.200
Exposure Characterization	4. Measurement of Exposure	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.	Medium	2	0.400	0.800
	5. Exposure levels	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.	Low	3	0.200	0.600
	6. Temporality	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.	Medium	2	0.400	0.800

N-Methyl-2-pyrrolidone

Study reference:	Haufroid, V.,Jaeger, V. K.,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 HERO ID: 2654929					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	7. Outcome measurement or characterization	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).	Medium	2	0.670	1.333
	8. Reporting Bias	Clinical outcomes are briefly qualitatively described, and thus cannot be extracted. The outcome biomarkers are fully reported.	Medium	2	0.330	0.667
Potential Counfounding/Variable Control	9. Covariate Adjustment	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.	Low	3	0.500	1.500
	10. Covariate Characterization	Smoking status/history determined with questionnaire. Other covariates assumed to be collected from employment records, but this is not explicitly states.	Medium	2	0.250	0.500
	11. Co-exposure Confounding	Categorized based on exposure to additional organic solvents. Hand washing with organic solvents also noted on the day of biomonitoring data collection.	Medium	2	0.250	0.500
Analysis	12. Study Design and Methods	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.	Medium	2	0.400	0.800
	13. Statistical power	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.	Medium	2	0.200	0.400

N-Methyl-2-pyrrolidone

Study reference:	Haufroid, V.,Jaeger, V. K.,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 HERO ID: 2654929					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	14. Reproducibility of analyses	Description of analysis sufficient to understand and reproduce.	Medium	2	0.200	0.400
	15. Statistical models	Multiple linear regression models used for exposed group and for the entire group for 2-HSMI/5-HNMP and s-creatinine.	Medium	2	0.200	0.400
Other	16. Use of Biomarker of Exposure	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.	High	1	0.140	0.143
	17. Effect biomarker	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.	Medium	2	0.140	0.286
	18. Method Sensitivity	Metabolites measured with LC-MS/MS and a LOQ of 0.2 mg/L.	Medium	2	0.140	0.286
Confounding / Variable Control	19. Biomarker stability	Storage history not described, but do not have a high likelihood of biomarker instability.	Medium	2	0.140	0.286
	20. Sample contamination	Blanks used for NMP metabolites, but no documentation of steps used to ensure contamination free from collection to measurement.	Low	3	0.140	0.429
Data Presentation and Analysis	21. Method requirements	LC-MS/MS used for NMP metabolites	High	1	0.140	0.143

N-Methyl-2-pyrrolidone

Study reference:	**Haufroid, V.,Jaeger, V. K.,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** **HERO ID: 2654929**					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Matrix adjustment	Creatinine adjusted and unadjusted values provided (Table 2).	High	1	0.140	0.143
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**6**	**11.82**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**NA**	**Overall Score: Nearest *:**	**NA**
		Overall Quality Level:		**Low**		
Study Quality Comment:	**The reviewer downgraded this study's overall quality rating. They did not provide an explanation. Note: The original calculated score for this study was 2.0. This value is not presented above because the final rating was changed based on professional judgement.**					

1.3. Epidemiological evaluation results of the Haufroid et al 2014 study for hepatic outcomes for cross-sectional occupational liver

Study reference:	Haufroid, V.,Jaeger, V. K.,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 HERO ID: 2654929					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	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)	High	1	0.400	0.400
	2. Attrition	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.	Medium	2	0.400	0.800
	3. Comparison Group	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.	High	1	0.200	0.200
Exposure Characterization	4. Measurement of Exposure	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.	Medium	2	0.400	0.800
	5. Exposure levels	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.	Low	3	0.200	0.600
	6. Temporality	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.	Medium	2	0.400	0.800

N-Methyl-2-pyrrolidone

Study reference:	Haufroid, V.,Jaeger, V. K.,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 HERO ID: 2654929					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	7. Outcome measurement or characterization	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).	Medium	2	0.670	1.333
	8. Reporting Bias	Clinical outcomes are briefly qualitatively described, and thus cannot be extracted. The outcome biomarkers are fully reported.	Medium	2	0.330	0.667
Potential Confounding/Variable Control	9. Covariate Adjustment	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.	Low	3	0.500	1.500
	10. Covariate Characterization	Smoking status/history determined with questionnaire. Other covariates assumed to be collected from employment records, but this is not explicitly states.	Medium	2	0.250	0.500
	11. Co-exposure Confounding	Categorized based on exposure to additional organic solvents. Hand washing with organic solvents also noted on the day of biomonitoring data collection.	Medium	2	0.250	0.500
Analysis	12. Study Design and Methods	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.	Medium	2	0.400	0.800
	13. Statistical power	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.	Medium	2	0.200	0.400

N-Methyl-2-pyrrolidone

Study reference:	Haufroid, V.,Jaeger, V. K.,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 HERO ID: 2654929					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	14. Reproducibility of analyses	Description of analysis sufficient to understand and reproduce.	Medium	2	0.200	0.400
	15. Statistical models	Multiple linear regression models used for exposed group and for the entire group for 2-HSMI/5-HNMP and GGT.	Medium	2	0.200	0.400
Other	16. Use of Biomarker of Exposure	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.	High	1	0.140	0.143
	17. Effect biomarker	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.	Medium	2	0.140	0.286
	18. Method Sensitivity	Metabolites measured with LC-MS/MS and a LOQ of 0.2 mg/L.	Medium	2	0.140	0.286
Confounding / Variable Control	19. Biomarker stability	Storage history not described, but do not have a high likelihood of biomarker instability.	Medium	2	0.140	0.286
	20. Sample contamination	Blanks used for NMP metabolites, but no documentation of steps used to ensure contamination free from collection to measurement.	Low	3	0.140	0.429
Data Presentation and Analysis	21. Method requirements	LC-MS/MS used for NMP metabolites	High	1	0.140	0.143

N-Methyl-2-pyrrolidone

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Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Matrix adjustment	Creatinine adjusted and unadjusted values provided (Table 2).	High	1	0.140	0.143
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**6**	**11.82**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.97**	**Overall Score: Nearest *:**	**2**
		Overall Quality Level:		**Medium**		
Study Quality Comment:	**The reviewer agreed with this study's overall quality level.**					

1.4. Epidemiological evaluation results of the Haufroid et al 2014 study for respiratory outcomes for cross-sectional occupational lung

Study reference:	**Haufroid, V.,Jaeger, V. K.,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** **HERO ID: 2654929**					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	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)	High	1	0.400	0.400
	2. Attrition	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.	Medium	2	0.400	0.800
	3. Comparison Group	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.	High	1	0.200	0.200
Exposure Characterization	4. Measurement of Exposure	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.	Medium	2	0.400	0.800
	5. Exposure levels	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.	Low	3	0.200	0.600
	6. Temporality	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.	Medium	2	0.400	0.800

N-Methyl-2-pyrrolidone

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Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	7. Outcome measurement or characterization	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).	Medium	2	0.670	1.333
	8. Reporting Bias	Clinical outcomes are briefly qualitatively described, and thus cannot be extracted. The outcome biomarkers are fully reported.	Medium	2	0.330	0.667
Potential Counfounding/Variable Control	9. Covariate Adjustment	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.	Low	3	0.500	1.500
	10. Covariate Characterization	Smoking status/history determined with questionnaire. Other covariates assumed to be collected from employment records, but this is not explicitly states.	Medium	2	0.250	0.500
	11. Co-exposure Confounding	Categorized based on exposure to additional organic solvents. Hand washing with organic solvents also noted on the day of biomonitoring data collection.	Medium	2	0.250	0.500
Analysis	12. Study Design and Methods	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.	Medium	2	0.400	0.800
	13. Statistical power	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.	Medium	2	0.200	0.400

N-Methyl-2-pyrrolidone

Study reference:	Haufroid, V.,Jaeger, V. K.,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 HERO ID: 2654929					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	14. Reproducibility of analyses	Description of analysis sufficient to understand and reproduce.	Medium	2	0.200	0.400
	15. Statistical models	Multiple linear regression models used for exposed group and for the entire group for some outcome but not FEV1.	Low	3	0.200	0.600
Other	16. Use of Biomarker of Exposure	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.	High	1	0.140	0.143
	17. Effect biomarker	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.	Medium	2	0.140	0.286
	18. Method Sensitivity	Metabolites measured with LC-MS/MS and a LOQ of 0.2 mg/L.	Medium	2	0.140	0.286
Confounding / Variable Control	19. Biomarker stability	Storage history not described, but do not have a high likelihood of biomarker instability.	Medium	2	0.140	0.286
	20. Sample contamination	Blanks used for NMP metabolites, but no documentation of steps used to ensure contamination free from collection to measurement.	Low	3	0.140	0.429
Data Presentation and Analysis	21. Method requirements	LC-MS/MS used for NMP metabolites	High	1	0.140	0.143

N-Methyl-2-pyrrolidone

Study reference:	Haufroid, V.,Jaeger, V. K.,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 HERO ID: 2654929					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Matrix adjustment	Creatinine adjusted and unadjusted values provided (Table 2).	High	1	0.140	0.143
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**6**	**12.02**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**NA**	**Overall Score: Nearest *:**	**NA**
		Overall Quality Level:		**Low**		
Study Quality Comment:	**The reviewer downgraded this study's overall quality rating. They did not provide an explanation. Note: The original calculated score for this study was 2.0. This value is not presented above because the final rating was changed based on professional judgement.**					

1.5. Epidemiological evaluation results of the Nishimura et al 2009 study for musculoskeletal/motor function outcomes for cross-sectional occupational

Study reference:	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 HERO ID: 735269					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	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.	Low	3	0.400	1.200
	2. Attrition	One exposed worked excluded from study, because he missed work on the day of health effects exam.	High	1	0.400	0.400
	3. Comparison Group	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.	High	1	0.200	0.200
Exposure Characterization	4. Measurement of Exposure	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 (Xiaofei et al., 2000) for details.	High	1	0.400	0.400
	5. Exposure levels	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.	Low	3	0.200	0.600
	6. Temporality	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.	Low	3	0.400	1.200

N-Methyl-2-pyrrolidone

Study reference:	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 HERO ID: 735269					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	7. Outcome measurement or characterization	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.	Medium	2	0.670	1.333
	8. Reporting Bias	States that no significant differences were reported in symptoms related to irritation, but no data provided. All other outcomes fully reported and extractable.	Medium	2	0.330	0.667
Potential Counfounding/Variable Control	9. Covariate Adjustment	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.	Medium	2	0.500	1.000
	10. Covariate Characterization	Smoking and medical histories collected from self-administered questionnaires. Source of age, body weight information not stated.	Medium	2	0.250	0.500
	11. Co-exposure Confounding	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).	Medium	2	0.250	0.500
Analysis	12. Study Design and Methods	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.	Medium	2	0.400	0.800
	13. Statistical power	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.	Medium	2	0.200	0.400

N-Methyl-2-pyrrolidone

Study reference:	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 HERO ID: 735269					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	14. Reproducibility of analyses	Simple analysis is reproducible.	Medium	2	0.200	0.400
	15. Statistical models	Means with standard deviations presented for outcomes. Regression models not discussed in detail, but not reported either. The presented analysis is sufficient.	Medium	2	0.200	0.400
Other	16. Use of Biomarker of Exposure	NMP was used as a biomarker, not its metabolites. Previous study showed that it can be reflective of exposure (Bader et al., 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.	Medium	2	0.170	0.333
	17. Effect biomarker	Biomarker not used for effects.	Not Rated	NA	NA	NA
	18. Method Sensitivity	LOD stated and sufficiently low to detect biomarker in all exposed samples.	Medium	2	0.170	0.333
Confounding / Variable Control	19. Biomarker stability	Urine samples stored at 4C, which differs from the 80C stated in the method reference (Xiaofei et al., 2000). Stability and time between collection and analysis not stated in either study.	Medium	2	0.170	0.333
	20. Sample contamination	Aside from requesting that participants washed their hands before providing samples, no information is provided regarding contamination.	Medium	2	0.170	0.333
Data Presentation and Analysis	21. Method requirements	GC-MS used for high degree of confidence in chemical identification.	Medium	2	0.170	0.333

Study reference:	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 HERO ID: 735269					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Matrix adjustment	Creatinine adjusted and unadjusted values provided (Table 2).	High	1	0.170	0.167
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**6**	**11.82**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.97**	**Overall Score: Nearest *:**	**2**
		Overall Quality Level:		**Medium**		
Study Quality Comment:	**The reviewer agreed with this study's overall quality level.**					

1.6. Epidemiological evaluation results of the Nishimura et al 2009 study for neurological/behavior outcomes in general

Study reference:	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 HERO ID: 735269						
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	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.	Low	3	0.400	1.200
	2. Attrition	One exposed worked excluded from study, because he missed work on the day of health effects exam.	High	1	0.400	0.400
	3. Comparison Group	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.	High	1	0.200	0.200
Exposure Characterization	4. Measurement of Exposure	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 (Xiaofei et al., 2000) for details.	High	1	0.400	0.400
	5. Exposure levels	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.	Low	3	0.200	0.600
	6. Temporality	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.	Low	3	0.400	1.200

N-Methyl-2-pyrrolidone

Study reference:	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 HERO ID: 735269					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	7. Outcome measurement or characterization	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.	Medium	2	0.670	1.333
	8. Reporting Bias	States that no significant differences were reported in symptoms related to irritation, but no data provided. All other outcomes fully reported and extractable.	Medium	2	0.330	0.667
Potential Counfounding/Variable Control	9. Covariate Adjustment	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.	Medium	2	0.500	1.000
	10. Covariate Characterization	Smoking and medical histories collected from self-administered questionnaires. Source of age, body weight information not stated.	Medium	2	0.250	0.500
	11. Co-exposure Confounding	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).	Medium	2	0.250	0.500
Analysis	12. Study Design and Methods	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.	Medium	2	0.400	0.800
	13. Statistical power	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.	Medium	2	0.200	0.400

N-Methyl-2-pyrrolidone

Study reference:	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 HERO ID: 735269					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	14. Reproducibility of analyses	Simple analysis is reproducible.	Medium	2	0.200	0.400
	15. Statistical models	Means with standard deviations presented for outcomes. Regression models not discussed in detail, but not reported either. The presented analysis is sufficient.	Medium	2	0.200	0.400
Other	16. Use of Biomarker of Exposure	NMP was used as a biomarker, not its metabolites. Previous study showed that it can be reflective of exposure (Bader et al., 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.	Medium	2	0.170	0.333
	17. Effect biomarker	Biomarker not used for effects.	Not Rated	NA	NA	NA
	18. Method Sensitivity	LOD stated and sufficiently low to detect biomarker in all exposed samples.	Medium	2	0.170	0.333
Confounding / Variable Control	19. Biomarker stability	Urine samples stored at 4C, which differs from the 80C stated in the method reference (Xiaofei et al., 2000). Stability and time between collection and analysis not stated in either study.	Medium	2	0.170	0.333
	20. Sample contamination	Aside from requesting that participants washed their hands before providing samples, no information is provided regarding contamination.	Medium	2	0.170	0.333
Data Presentation and Analysis	21. Method requirements	GC-MS used for high degree of confidence in chemical identification.	Medium	2	0.170	0.333

N-Methyl-2-pyrrolidone

Study reference:	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 HERO ID: 735269					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Matrix adjustment	Creatinine adjusted and unadjusted values provided (Table 2).	High	1	0.170	0.167
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**6**	**11.82**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.97**	**Overall Score: Nearest *:**	**2**
		Overall Quality Level:		**Medium**		
Study Quality Comment:	**The reviewer agreed with this study's overall quality level.**					

References

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