United States
Environmental Protection Agency

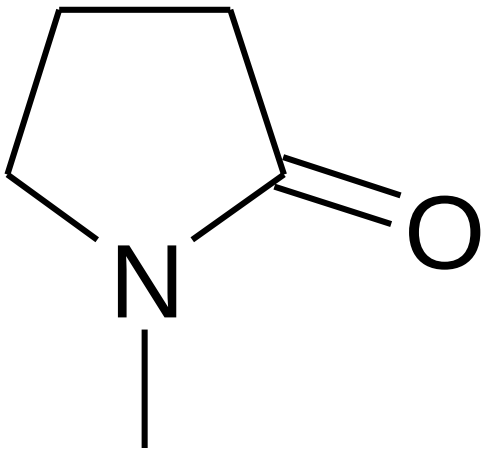
Office of Chemical Safety and
Pollution Prevention

Risk Evaluation for N-Methylpyrrolidone

Systematic Review Supplemental File:

Data Quality Evaluation of Human Health Hazard Studies – Animal Studies

CASRN: 872-50-4



October 2019

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1. Acute and Short-Term Toxicity Studies

1.1. Animal toxicity evaluation results of Boenisch et al 2012 for a 19-day immunotoxicity (inhalation) study on hematological, immune, and respiratory outcomes

Study reference:	**Boenisch, U.,Boehme, A.,Kohajda, T.,Moegel, I.,Schuetze, N.,von Bergen, M.,Simon, J.,Lehmann, I.,Polte, T. (2012). Volatile Organic Compounds Enhance Allergic Airway Inflammation in an Experimental Mouse Model PLoS ONE, 7(7), e39817** **HERO ID: 2333837**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	See footnote at end of page.[1].	High	1	2	2
	2. Test Substance Source	The source and batch/lot number of the test substance was not reported.	Low	3	1	3
	3. Test Substance Purity	Purity and grade of the test substance were not reported.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	The study authors reported using a concurrent negative control group.	High	1	2	2
	5. Positive Controls	Positive controls were not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	The study authors did not report how animals were allocated to study groups.	Low	3	1	3
Exposure Characteriz[1]ation	7. Preparation and Storage of Test Substance	The study authors did not describe the test substance preparation or storage conditions. The reporting deficiencies are likely to have a substantial impact on results.	Low	3	1	3
	8. Consistency of Exposure Administration	Critical exposure details, including the methods for generating atmosphere in inhalation chambers, were not reported.	Low	3	1	3

[1] Metric that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	**Boenisch, U.,Boehme, A.,Kohajda, T.,Moegel, I.,Schuetze, N.,von Bergen, M.,Simon, J.,Lehmann, I.,Polte, T. (2012). Volatile Organic Compounds Enhance Allergic Airway Inflammation in an Experimental Mouse Model PLoS ONE, 7(7), e39817** **HERO ID: 2333837**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	9. Reporting of Doses/Concentrations[1]	Mean concentrations were measured (as reported in supplemental file S1).	Medium	2	2	4
	10. Exposure Frequency and Duration	The exposure duration and frequency were reported and were suitable for the study type (the animals were exposed in a whole-body inhalation chamber from days 0-19 or days 17-19).	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups and spacing were reported and were relevant for the assessment.	High	1	1	1
	12. Exposure Route and Method	The exposure route and method of exposure (whole body) were reported; however, there were reporting deficiencies in the chamber (e.g., number of changes per hour).	Low	3	1	3
Test Organism	13. Test Animal Characteristics	Ovalbumin-sensitized and non-sensitized mice were used. The body weight, and health status of mice at the start of the study were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	All husbandry conditions were reported and were adequate and the same for the control and exposed populations.	High	1	1	1

[1] Metric that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	**Boenisch, U.,Boehme, A.,Kohajda, T.,Moegel, I.,Schuetze, N.,von Bergen, M.,Simon, J.,Lehmann, I.,Polte, T. (2012). Volatile Organic Compounds Enhance Allergic Airway Inflammation in an Experimental Mouse Model PLoS ONE, 7(7), e39817** **HERO ID: 2333837**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	15. Number per Group	The number per group was not clearly reported in the methods (other than stating that all animal experiments involved groups of 4-6 mice/cage). However, the results appear to have been based on at least 9 animals per group (e.g., see Figures 4, 6A), although some results were based on only 4 animals (e.g., Fig 6B, 6C).	Low	3	1	3
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology addressed or reported the intended outcomes of interest and was sensitive for the outcomes of interest.	High	1	2	2
	17. Consistency of Outcome Assessment	Details of the outcome assessment protocol were reported, and outcomes were assessed consistently across study groups.	High	1	1	1
	18. Sampling Adequacy	Sampling of the outcomes of interest were adequate.	High	1	1	1
	19. Blinding of Assessors	Blinding is not required for objective outcomes.	Not Rated	NA	NA	NA
	20. Negative Control Response	The negative control responses were reported and acceptable.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Respiratory rate measurement was not reported. This is may impact results since NMP is a potential respiratory irritant.	Low	3	2	6

Study reference:	**Boenisch, U.,Boehme, A.,Kohajda, T.,Moegel, I.,Schuetze, N.,von Bergen, M.,Simon, J.,Lehmann, I.,Polte, T. (2012). Volatile Organic Compounds Enhance Allergic Airway Inflammation in an Experimental Mouse Model PLoS ONE, 7(7), e39817** **HERO ID: 2333837**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Health Outcomes Unrelated to Exposure	Data on attrition and health outcomes unrelated to exposure were not reported for each study group and this deficiency may have a substantial impact on results.	Low	3	1	3
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were reported and were appropriate for the data sets.	High	1	1	1
	24. Reporting of Data	Data for exposure-related findings were presented for all outcomes by exposure group with quantal or continuous presentation. Negative findings were reported qualitatively and/or quantitatively.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**53**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.8276**	**Overall Score: Nearest *:**	**1.8**
		Overall Quality Level:		**Medium**		

1.1. Animal toxicity evaluation results of E.I. DuPont De Nemours & Co. 1991 for a 4-week inhalation, mortality, and histopathology study on respiratory, endocrine, hematological, and immune outcomes

Study reference:	**E. I. DuPont De Nemours & Co (1991). Initial submission: four-week inhalation range-finding test on 1-methyl-2-pyrrolidone (final report) with attachments and cover letter dated 112691, 920000398, #88-920000398** **HERO ID: 3563360**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	See footnote at end of page.[1]	High	1	2	2
	2. Test Substance Source	Test substance submitted by identified persons.	Low	3	1	3
	3. Test Substance Purity	Purity was not reported.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	Concurrent controls were used.	High	1	2	2
	5. Positive Controls	Positive controls were not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Randomized allocation of animals was not reported.	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Methods and equipment used to generate the aerosol were reported; however, storage of the test material was not reported.	Medium	2	1	2
	8. Consistency of Exposure Administration	Exposures were administered consistently.	High	1	1	1
	9. Reporting of Doses/Concentrations	Nominal and measured concentrations were reported, but particle size and MMAD were not reported.	Low	3	2	6
	10. Exposure Frequency and Duration	Duration was reported, but frequency, in terms of days/week, was reported only as 21 six-hour exposures	Medium	2	1	2
	11. Number of Exposure Groups and Dose Spacing	The number of groups and spacing were reported and justified.	High	1	1	1
	12. Exposure Route and Method	The number of air changes in the exposure chamber was not reported.	Low	3	1	3

Study reference:	E. I. DuPont De Nemours & Co (1991). Initial submission: four-week inhalation range-finding test on 1-methyl-2-pyrrolidone (final report) with attachments and cover letter dated 112691, 920000398, #88-920000398 HERO ID: 3563360					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Organism	13. Test Animal Characteristics	The species, strain, sex, and initial body weight were reported. The age, health status, and source were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Husbandry conditions were not reported.	Low	3	1	3
	15. Number per Group	The number of animals per group was appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Breathing rates and body temperature were not measured to rule out reflex bradypnea from irritancy.	Low	3	2	6
	17. Consistency of Outcome Assessment	Outcomes were assessed consistently.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate.	High	1	1	1
	19. Blinding of Assessors	Blinding was not required.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative controls responded appropriately.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Test animals showed signs of lethargy and irregular respiration which persisted until the end of each exposure.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	No health outcomes unrelated to exposures were reported.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were described in the appendices and were appropriate. Analysis of histopathological results was not conducted.	Medium	2	1	2
	24. Reporting of Data	Data were reported.	High	1	2	2
		Sum of scores:			**29**	**56**

Study reference:	E. I. DuPont De Nemours & Co (1991). Initial submission: four-week inhalation range-finding test on 1-methyl-2-pyrrolidone (final report) with attachments and cover letter dated 112691, 920000398, #88-920000398 HERO ID: 3563360					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		1.9310	Overall Score: Nearest *:	1.9
		Overall Quality Level:		Medium		

1.2. Animal toxicity evaluation results of Gopinathan et al 2013 for a 5-day oral study on clinical chemistry/biochemical, renal, hematological and immune outcomes

Study reference:	**Gopinathan, S.,O'Neill, E.,Rodriguez, L. A.,Champ, R.,Phillips, M.,Nouraldeen, A. mr,Wendt, M.,Wilson, A. G. E.,Kramer, J. A. (2013). In vivo toxicology of excipients commonly employed in drug discovery in rats Journal of Pharmacological and Toxicological Methods, 68(2), 284-295** **HERO ID: 3037621**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	The test substance was identified.	Medium	2	2	4
	2. Test Substance Source	The source of the test substance was reported, but a batch/lot number was not reported.	Medium	2	1	2
	3. Test Substance Purity	Test substance purity was not reported, but all substances tested in the study were stated to have been of reagent or pharmacopeia grade.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	The study authors reported using a concurrent negative control group; however, details were not fully reported on the negative control group (whether the negative control received the same preparation as used for the test substance (e.g., vehicle).	Low	3	2	6
	5. Positive Controls	Positive controls were not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	The study reported methods of allocation of animals to study groups, but minor limitations were observed in that animals were randomly stratified by body weight.	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Preparation and storage of the test substance were not reported.	Low	3	1	3

Study reference:	**Gopinathan, S.,O'Neill, E.,Rodriguez, L. A.,Champ, R.,Phillips, M.,Nouraldeen, A. mr,Wendt, M.,Wilson, A. G. E.,Kramer, J. A. (2013). In vivo toxicology of excipients commonly employed in drug discovery in rats Journal of Pharmacological and Toxicological Methods, 68(2), 284-295** **HERO ID: 3037621**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	8. Consistency of Exposure Administration	Details of the exposure administration were reported, and exposures were administered consistently across study groups in a scientifically sound manner (e.g., dose volume was acceptable).	High	1	1	1
	9. Reporting of Doses/Concentrations	Administered doses were reported without ambiguity.	High	1	2	2
	10. Exposure Frequency and Duration	The exposure frequency and duration were reported and were appropriate for the study type and outcomes of interest (acute toxicity).	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups and dose spacing was reported and was acceptable.	High	1	1	1
	12. Exposure Route and Method	The exposure route and method were reported and were acceptable.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The test animal source, species, strain, and sex were reported; however, age, health status, and starting body weights were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Most husbandry conditions (e.g., temperature, light cycle, housing) were reported and were adequate and similar for all groups; however, humidity levels were not reported.	Low	3	1	3
	15. Number per Group	The number of animals per group (5 males/group) was reported, appropriate for the study type and outcome analysis, and consistent with studies of the same or similar type.	High	1	1	1

Study reference:	**Gopinathan, S.,O'Neill, E.,Rodriguez, L. A.,Champ, R.,Phillips, M.,Nouraldeen, A. mr,Wendt, M.,Wilson, A. G. E.,Kramer, J. A. (2013). In vivo toxicology of excipients commonly employed in drug discovery in rats Journal of Pharmacological and Toxicological Methods, 68(2), 284-295** **HERO ID: 3037621**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology addressed or reported the intended outcomes of interest and was sensitive for the outcomes of interest (acute effects).	High	1	2	2
	17. Consistency of Outcome Assessment	Details of the outcome assessment methodology were reported, and outcomes were assessed consistently across study groups using the same protocol for all groups.	High	1	1	1
	18. Sampling Adequacy	Details regarding sampling for the outcomes of interest were reported and the study used adequate sampling for the outcomes of interest.	High	1	1	1
	19. Blinding of Assessors	Blinding was not required.	Not Rated	NA	NA	NA
	20. Negative Control Response	The negative control responses were reported and acceptable.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	There were no reported differences among the study groups that would influence the outcome.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	Data on attrition and health outcomes unrelated to exposure were not reported for each study group and this deficiency may have a substantial impact on results.	Low	3	1	3
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were clearly described and were appropriate for the data sets.	High	1	1	1

Study reference:	**Gopinathan, S.,O'Neill, E.,Rodriguez, L. A.,Champ, R.,Phillips, M.,Nouraldeen, A. mr,Wendt, M.,Wilson, A. G. E.,Kramer, J. A. (2013). In vivo toxicology of excipients commonly employed in drug discovery in rats Journal of Pharmacological and Toxicological Methods, 68(2), 284-295** **HERO ID: 3037621**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	24. Reporting of Data	Data for exposure-related outcomes were reported for most, but not all, outcomes by exposure group. For example, mottled kidneys were observed in all treated groups with a combined incidence of 8/15 rats (not observed in the control group). The incidence of mottled kidneys observed by dose group were not reported.	Low	3	2	6
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**51**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.7586**	**Overall Score: Nearest *:**	**1.8**
		Overall Quality Level		**Medium**		

1.3. Animal toxicity evaluation results of Lashmar et al 1989 for an irritation study, dermal 24-hour study on irritation outcomes

Study reference:	**Lashmar, U. T.,Hadgraft, J.,Thomas, N. (1989). Topical application of penetration enhancers to the skin of nude mice: a histopathological study Journal of Pharmacy and Pharmacology, 41(2), 118-122** **HERO ID: 3539872**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance identified by name; CASRN not reported.	Medium	2	2	4
	2. Test Substance Source	The source manufacturer was reported, but batch/lot numbers were not; this omission is unlikely to have a substantial impact on results.	Medium	2	1	2
	3. Test Substance Purity	Test substance reported to be "reagent grade", but no specific purity was reported.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	A negative control group (untreated skin) was used; it is unclear if the untreated skin area was subjected to the same conditions as the exposed area. A 1% (w/w) neutralized carbomer gel was also tested as a control.	Medium	2	2	4
	5. Positive Controls	The use of a positive control is not indicated by this study type.	Not Rated	NA	NA	NA
	6. Randomized Allocation	The study did not report how animals were allocated to study groups.	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Test substance preparation was briefly reported. There is a lack of reporting of the test substance storage.	Low	3	1	3
	8. Consistency of Exposure Administration	Details of exposure protocol were limited; however, this deficiency is unlikely to have a substantial impact on the results.	Medium	2	1	2
	9. Reporting of Doses/Concentrations	Administered doses are reported.	High	1	2	2

Study reference:	**Lashmar, U. T.,Hadgraft, J.,Thomas, N. (1989). Topical application of penetration enhancers to the skin of nude mice: a histopathological study Journal of Pharmacy and Pharmacology, 41(2), 118-122** **HERO ID: 3539872**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Exposure Frequency and Duration	Exposure duration (24-hours) was reported and appropriate for the study.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups and the dose spacing were not justified by the study authors; however, the number of doses and spacing are adequate to show results relevant to the outcome of interest.	Medium	2	1	2
	12. Exposure Route and Method	The exposure route and method are appropriate and reported with limited detail; however, this deficiency is unlikely to have a substantial impact on the results.	Medium	2	1	2
Test Organism	13. Test Animal Characteristics	The test animal species, strain, sex, age, and starting body weight are reported, but there is no information on the health status of the mice reported. This omission in reporting is unlikely to have a substantial impact on results. It is unclear if this species (nude mouse) is an adequate animal model for the outcome of interest.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Animal husbandry conditions were not sufficiently reported to determine whether husbandry was adequate.	Low	3	1	3
	15. Number per Group	The number of animals per study group was reported (3) and appropriate for the study type.	High	1	1	1

N-Methylpyrrolidone

Study reference:	**Lashmar, U. T.,Hadgraft, J.,Thomas, N. (1989). Topical application of penetration enhancers to the skin of nude mice: a histopathological study Journal of Pharmacy and Pharmacology, 41(2), 118-122** **HERO ID: 3539872**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology was partially addressed for the intended outcomes of interest reported	Medium	2	2	4
	17. Consistency of Outcome Assessment	The assessment protocol were reported and consistent across study groups and chemicals tested.	High	1	1	1
	18. Sampling Adequacy	Details regarding sampling for the outcomes of interest were reported and adequate.	High	1	1	1
	19. Blinding of Assessors	This metric is not applicable for initial histopathology review; therefore, is not rated for this study.	Not Rated	NA	NA	NA
	20. Negative Control Response	The untreated control and 1% gel control response was adequate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	PVC and PVCD were used for occluded dermal exposure, it is unclear how this may have impacted the results.	Medium	2	2	4
	22. Health Outcomes Unrelated to Exposure	There is no reporting for attrition and/or health outcomes unrelated to exposure, though it is unlikely to have a substantial impact on results.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	No statistical analysis methods or statistical results were reported; however, calculation methods for irritation scores were described.	Medium	2	1	2

Study reference:	Lashmar, U. T.,Hadgraft, J.,Thomas, N. (1989). Topical application of penetration enhancers to the skin of nude mice: a histopathological study Journal of Pharmacy and Pharmacology, 41(2), 118-122 HERO ID: 3539872					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	24. Reporting of Data	Not all data was reported for the outcome. Only the model relative irritancy score for the representative tested animals. Irritation scores for individual animals was not reported for any exposure group. Histopathological results are presented qualitatively as images of skin sections.	Medium	2	2	4
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**28**	**55**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.9643**	**Overall Score: Nearest *:**	**2.0**
		Overall Quality Level:		**Medium**		

1.4. Animal toxicity evaluation results of Lee et al 1987 for a 4-week inhalation study on respiratory, hematological, and immune outcomes

Study reference:	**Lee, K. P.,Chromey, N. C.,Culik, R.,Barnes, J. R.,Schneider, P. W. (1987). Toxicity of N-methyl-2-pyrrolidone (NMP): teratogenic, subchronic, and two-year inhalation studies Fundamental and Applied Toxicology, 9(2), 222-235** **HERO ID: 3539878**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Structure, nomenclature, physiochemical properties provided	High	1	2	2
	2. Test Substance Source	Source not identified	Low	3	1	3
	3. Test Substance Purity	Purity such that effects due to test substance.	Medium	2	1	2
Test Design	4. Negative and Vehicle Controls	Negative controls were included	High	1	2	2
	5. Positive Controls	Positive controls not required	Not Rated	NA	NA	NA
	6. Randomized Allocation	Method of allocation was not described	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Preparation of test atmospheres was described, storage of the test material was not.	Medium	2	1	2
	8. Consistency of Exposure Administration	Exposures were administered consistently	High	1	1	1
	9. Reporting of Doses/Concentrations	Aerosol particle size and MMAD were not reported.	Low	3	2	6
	10. Exposure Frequency and Duration	Duration of exposure did not extend throughout organogenesis.	Medium	2	1	2
	11. Number of Exposure Groups and Dose Spacing	Rationale for dose selection was not provided	Medium	2	1	2
	12. Exposure Route and Method	Route was appropriate, but insufficient detail was provided on the method (e.g., humidity, number of air changes per hour)	Low	3	1	3
Test Organism	13. Test Animal Characteristics	The source, species, strain, and sex were provided; age, and initial body weight, and health status were not reported.	Low	3	2	6

Study reference:	**Lee, K. P.,Chromey, N. C.,Culik, R.,Barnes, J. R.,Schneider, P. W. (1987). Toxicity of N-methyl-2-pyrrolidone (NMP): teratogenic, subchronic, and two-year inhalation studies Fundamental and Applied Toxicology, 9(2), 222-235** **HERO ID: 3539878**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	14. Adequacy and Consistency of Animal Husbandry Conditions	Husbandry was not adequately reported.	Low	3	1	3
	15. Number per Group	The number of animals exposed in each group was adequate	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Breathing rate and body temperature were not measured.	Low	3	2	6
	17. Consistency of Outcome Assessment	Outcomes were assessed consistently.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate for the outcomes	High	1	1	1
	19. Blinding of Assessors	Subjective outcomes were not assessed	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative controls responded appropriately	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Test animals showed signs of lethargy and irregular respiration.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	None were reported	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were appropriate when applied, but all outcomes were not analyzed.	Medium	2	1	2
	24. Reporting of Data	Data were reported for outcomes	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**57**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.9655**	**Overall Score: Nearest *:**	**2.0**
		Overall Quality Level:		**Medium**		

1.5. Animal toxicity evaluation results of Malek et al 1997 for a 28-day oral, rats and mice study on renal, hematology, and histopathology of various organs

Study reference:	Malek, D. E.,Malley, L. A.,Slone, T. W.,Elliott, G. S.,Kennedy, G. L.,Mellert, W.,Deckardt, K.,Gembardt, C.,Hildebrand, B.,Murphy, S. R.,Bower, D. B.,Wright, G. A. (1997). Repeated dose toxicity study (28 days) in rats and mice with N-methylpyrrolidone (NMP) Drug and Chemical Toxicology, 20(1-2), 63-77 HERO ID: 3539910					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance identified by name and CASRN.	High	1	2	2
	2. Test Substance Source	The source was identified.	High	1	1	1
	3. Test Substance Purity	The reported purity was such that effects likely due to the test substance.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Concurrent negative control animals were included.	High	1	2	2
	5. Positive Controls	Positive controls not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Animals were allocated by computerized stratified randomization so no statistically significant differences among body weights were observed.	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Limited preparation details were presented; however, no information on NMP analytical concentration, storage or stability were reported.	Low	3	1	3
	8. Consistency of Exposure Administration	Exposures were administered consistently.	High	1	1	1
	9. Reporting of Doses/Concentrations	Doses were reported.	High	1	2	2
	10. Exposure Frequency and Duration	Frequency and duration of exposure were reported.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups and spacing were reported and justified.	High	1	1	1
	12. Exposure Route and Method	The exposure route and method were appropriate.	High	1	1	1

Study reference:	**Malek, D. E.,Malley, L. A.,Slone, T. W.,Elliott, G. S.,Kennedy, G. L.,Mellert, W.,Deckardt, K.,Gembardt, C.,Hildebrand, B.,Murphy, S. R.,Bower, D. B.,Wright, G. A. (1997). Repeated dose toxicity study (28 days) in rats and mice with N-methylpyrrolidone (NMP) Drug and Chemical Toxicology, 20(1-2), 63-77** **HERO ID: 3539910**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Organism	13. Test Animal Characteristics	The source, species, strain, sex, age, and initial body weight, and health status were reported.	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	All husbandry conditions except room air changes were reported.	Medium	2	1	2
	15. Number per Group	The numbers of animals per group were appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Outcome assessment methodology was appropriate.	High	1	2	2
	17. Consistency of Outcome Assessment	Outcomes were assessed consistently.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate.	High	1	1	1
	19. Blinding of Assessors	Blinding was not required.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses were appropriate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables were reported.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	No health effects unrelated to exposure were reported.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were reported and appropriate.	High	1	1	1
	24. Reporting of Data	Data were reported.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**28**	**33**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.1786**	**Overall Score: Nearest *:**	**1.2**

Study reference:	Malek, D. E.,Malley, L. A.,Slone, T. W.,Elliott, G. S.,Kennedy, G. L.,Mellert, W.,Deckardt, K.,Gembardt, C.,Hildebrand, B.,Murphy, S. R.,Bower, D. B.,Wright, G. A. (1997). Repeated dose toxicity study (28 days) in rats and mice with N-methylpyrrolidone (NMP) Drug and Chemical Toxicology, 20(1-2), 63-77 HERO ID: 3539910					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
		Overall Quality Level:		**High**		

1.6. Animal toxicity evaluation results of N-Methylpyrrolidone Producers Group (1994) for a 4-week dietary study in mice on mortality; nutrition and metabolic/adult exposure body weight; renal; hepatic; hematological and immune; clinical chemistry/biochemical; ADME/PBPK and reproductive (male) outcomes

Study reference:	**N-Methylpyrrolidone Producers Group, Inc (1994). Repeated dose toxicity with N-Methylpyrrolidone in B6C3F1 mice Administration in the diet for 4 weeks (Range-finding study)** **HERO ID: 4214115**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	The test substance was identified definitely and CASRN reported.	High	1	2	2
	2. Test Substance Source	The source of the testing laboratory (industry sponsored) test substance was reported, including manufacturer and batch/lot number.	High	1	1	1
	3. Test Substance Purity	The test substance purity was reported.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Study authors reported using an appropriate concurrent negative control group.	High	1	2	2
	5. Positive Controls	Not required for study type	Not Rated	NA	NA	NA
	6. Randomized Allocation	Randomization list was drawn up by a computer based on body weight (laboratory data processing, Dept of Toxicology, BASF)	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	The test substance preparation and storage conditions were reported and appropriate for the test substance.	High	1	1	1
	8. Consistency of Exposure Administration	Details of exposure administration were reported, and exposures were administered consistently across study groups.	High	1	1	1

Study reference:	N-Methylpyrrolidone Producers Group, Inc (1994). Repeated dose toxicity with N-Methylpyrrolidone in B6C3F1 mice Administration in the diet for 4 weeks (Range-finding study) HERO ID: 4214115					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	9. Reporting of Doses/Concentrations	The study authors reported the administered doses/concentrations, including the calculated information from ppm in diet to mg/kg-day in the diet for all the exposed groups without ambiguity.	High	1	2	2
	10. Exposure Frequency and Duration	The exposure frequency and duration of exposure were reported.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups (n=4) and dose/concentration spacing were justified by study authors and considered adequate to address the purpose of the study.	High	1	1	1
	12. Exposure Route and Method	The route and method of exposure were reported and were suited to the test substance.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The test animal species, strain, sex, health status, age, and starting body weight were reported and the test animal was obtained from a commercial source or laboratory-maintained colony.	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	The study authors reported all husbandry conditions and were adequate and the same for control and exposed populations, such that the only difference was exposure.	High	1	1	1
	15. Number per Group	The reported number of animals per study group was lower than the typical number used in studies of the same or similar type.	Medium	2	1	2

Study reference:	N-Methylpyrrolidone Producers Group, Inc (1994). Repeated dose toxicity with N-Methylpyrrolidone in B6C3F1 mice Administration in the diet for 4 weeks (Range-finding study) HERO ID: 4214115					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology addressed or reported the intended outcome(s) of interest and was sensitive for the outcomes(s) of interest.	High	1	2	2
	17. Consistency of Outcome Assessment	incomplete reporting of minor details of outcome assessment protocol execution, but these uncertainties or limitations are unlikely to have a substantial impact on results.	Medium	2	1	2
	18. Sampling Adequacy	Details regarding sampling for the outcome(s) of interest were reported and the study used adequate sampling for the outcome(s) of interest.	High	1	1	1
	19. Blinding of Assessors	The study did not report whether assessors were blinded to treatment group for subjective outcomes, and this deficiency is likely to have a substantial impact on results.	Low	3	1	3
	20. Negative Control Response	The biological responses of the negative control group(s) were adequate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	There were no reported differences among the study groups in initial body weight, food intake, or respiratory rate that could influence the outcome assessment. The authors did not report water intake, but it is not likely to have a significant impact on results.	High	1	2	2

Study reference:	N-Methylpyrrolidone Producers Group, Inc (1994). Repeated dose toxicity with N-Methylpyrrolidone in B6C3F1 mice Administration in the diet for 4 weeks (Range-finding study) HERO ID: 4214115					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Health Outcomes Unrelated to Exposure	Details regarding animal attrition and health outcomes unrelated to exposure were reported for each study group.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were clearly described and appropriate for dataset(s).	High	1	1	1
	24. Reporting of Data	Data for exposure-related findings were presented for all outcomes by exposure group.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**30**	**35**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.1739**	**Overall Score: Nearest *:**	**1.2**
		Overall Quality Level:		**High**		

1.7. Animal toxicity evaluation results of N-Methylpyrrolidone Producers Group et al 1994 for a 28-day diet rat-systemic and repro effects study on clinical chemistry/biochemical, body weight, hematological, immune, renal, endocrine, and reproductive outcomes

Study reference:	**N-Methylpyrrolidone Producers Group, Inc (1994). Subchronic Oral Toxicity: 28-day Feeding study in Rats with N-Methylpyrrolidone (NMP)** **HERO ID: 4214124**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance identified by name, synonyms, CASRN, form, and structure.	High	1	2	2
	2. Test Substance Source	The source was identified along with production date, and tank number.	High	1	1	1
	3. Test Substance Purity	Purity and composition are such that effects are likely due to the test substance.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Concurrent negative control animals were included.	High	1	2	2
	5. Positive Controls	Positive control animals not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Allocation wad by computerized stratified randomization to prevent no statistically significant differences among mean body weights by sex.	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Preparation and storage conditions were appropriate. Stability, homogeneity, and concentration analysis were conducted and appropriate.	High	1	1	1
	8. Consistency of Exposure Administration	Diets were administered consistently.	High	1	1	1
	9. Reporting of Doses/Concentrations	Doses were reported without ambiguity.	High	1	2	2
	10. Exposure Frequency and Duration	Exposure frequency and duration were reported.	High	1	1	1

Study reference:	N-Methylpyrrolidone Producers Group, Inc (1994). Subchronic Oral Toxicity: 28-day Feeding study in Rats with N-Methylpyrrolidone (NMP) HERO ID: 4214124					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups and dose spacing were based on the results of previous studies.	High	1	1	1
	12. Exposure Route and Method	The route and method were as specified in TPA TSCA testing consent order.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The source, species, strain, sex, age, initial body weight, and health status were reported.	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	All husbandry conditions were reported and were appropriate.	High	1	1	1
	15. Number per Group	The number of animals per group was appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Outcome assessment methodology was reported.	High	1	2	2
	17. Consistency of Outcome Assessment	Outcome assessment was consistent across groups.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate for the outcomes of interest.	High	1	1	1
	19. Blinding of Assessors	Blinding not required for the outcomes.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative controls responded appropriately.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	A palatability study was conducted prior to the study which reported that the dietary levels was likely to be tolerated by the rats in a 28-day study. No other confounding variables in test design or procedures were observed.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	No health outcomes unrelated to exposure were reported.	High	1	1	1

Study reference:	N-Methylpyrrolidone Producers Group, Inc (1994). Subchronic Oral Toxicity: 28-day Feeding study in Rats with N-Methylpyrrolidone (NMP) HERO ID: 4214124					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Data Presentation and Analysis	23. Statistical Methods	Statistical analyses were described and appropriate.	High	1	1	1
	24. Reporting of Data	All outcomes were reported.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**32**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.1034**	**Overall Score: Nearest *:**	**1.1**
		Overall Quality Level:		**High**		

1.8. Animal toxicity evaluation results of Tatsuno et al 2014 for an immunotoxicity study on immune outcomes

Study reference:	**Tatsuno, T.,Miyazaki, K.,Yamashiro, H. (2014). Multiple solvent, N-methyl-2-pyrrolidone, acts as a novel adjuvant for enhancing cutaneous immune responses Bioscience, Biotechnology, and Biochemistry, 78(6), 954-959** **HERO ID: 3540753**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance identified by name, but more information may be in reference describing preparation of test tapes.	Medium	2	2	4
	2. Test Substance Source	Source of test substance not identified.	Low	3	1	3
	3. Test Substance Purity	Purity not reported	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	Animals given a placebo were included.	High	1	2	2
	5. Positive Controls	Positive controls not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Method of randomized allocation was not reported.	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Preparation not reported.	Low	3	1	3
	8. Consistency of Exposure Administration	Exposures were administered consistently.	High	1	1	1
	9. Reporting of Doses/Concentrations	Percentages were reported.	Medium	2	2	4
	10. Exposure Frequency and Duration	See footnote at end of page.[1].	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of groups and spacing were reported only.	Medium	2	1	2
	12. Exposure Route and Method	See footnote at end of page.[2].	High	1	1	1

[1] Metrics that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

[2] Metrics that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	Tatsuno, T.,Miyazaki, K.,Yamashiro, H. (2014). Multiple solvent, N-methyl-2-pyrrolidone, acts as a novel adjuvant for enhancing cutaneous immune responses Bioscience, Biotechnology, and Biochemistry, 78(6), 954-959 HERO ID: 3540753					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Organism	13. Test Animal Characteristics	The source, species, strain, and age were reported. Health status and initial body weight were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Husbandry conditions were not reported.	Low	3	1	3
	15. Number per Group	The number of animals per group were appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	See footnote at end of page [1].	High	1	2	2
	17. Consistency of Outcome Assessment	See footnote at end of page [1].	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate.	High	1	1	1
	19. Blinding of Assessors	Blinding not required.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative and placebo responses were reported and appropriate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables were observed.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	No health outcomes unrelated to exposure were reported.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	See footnote at end of page [1].	High	1	1	1
	24. Reporting of Data	Outcome data were reported.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**28**	**46**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.5862**	**Overall Score: Nearest *:**	**1.6**
		Overall Quality Level:		High		

N-Methylpyrrolidone

2. Subchronic Toxicity Studies

2.1. Animal toxicity evaluation results of BASF 1995 for a 90-day diet mouse-liver toxicity study on hepatic outcomes

Study reference:	BASF (1995). N-METHYLPYRROLIDONE - SUBCHRONIC ORAL TOXICITY STUDY IN B6C3F1 MICE BY ADMINISTRATION IN THE DIET FOR 3 MONTHS, WITH COVER LETTER DATED 11/22/95 HERO ID: 3585204					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance identified by name and CASRN	High	1	2	2
	2. Test Substance Source	Source not identified but production container was listed.	Medium	2	1	2
	3. Test Substance Purity	Purity (99.8%) determined by gas chromatography and such that effects likely due to the test substance.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Concurrent negative controls were used.	High	1	2	2
	5. Positive Controls	Positive controls not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Animals allocated by weight using a computerized randomization list.	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Preparation and storage details were provided. Stability, homogeneity, and concentration tests were conducted.	High	1	1	1
	8. Consistency of Exposure Administration	Exposures were administered consistently.	High	1	1	1
	9. Reporting of Doses/Concentrations	Doses were reported.	High	1	2	2
	10. Exposure Frequency and Duration	Frequency and duration of exposures were reported.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of groups and dose spacing were reported and justified.	High	1	1	1
	12. Exposure Route and Method	Route and method were appropriate.	High	1	1	1

Study reference:	BASF (1995). N-METHYLPYRROLIDONE - SUBCHRONIC ORAL TOXICITY STUDY IN B6C3F1 MICE BY ADMINISTRATION IN THE DIET FOR 3 MONTHS, WITH COVER LETTER DATED 11/22/95 HERO ID: 3585204					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Organism	13. Test Animal Characteristics	The source, species, strain, sex, initial body weight, and health status were reported.	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	All husbandry conditions except air changes were reported.	Medium	2	1	2
	15. Number per Group	The number of animals per group was appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Outcome assessment methodology was appropriate.	High	1	2	2
	17. Consistency of Outcome Assessment	Outcomes were assessed consistently.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate.	High	1	1	1
	19. Blinding of Assessors	Blinding not required.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses were appropriate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables were observed.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	No health outcomes unrelated to exposure were observed.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical analysis was conducted and appropriate.	High	1	1	1
	24. Reporting of Data	Data were presented.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**33**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.1364**	**Overall Score: Nearest *:**	**1.1**
		Overall Quality Level:		**High**		

N-Methylpyrrolidone

2.2. Animal toxicity evaluation results of Malley et al 1999 for a 90-day oral rats and mice study on neurological/behavior, body weight, hepatic, and renal outcomes

Study reference:	**Malley, L. A.,Kennedy, G. L.,Elliott, G. S.,Slone, T. W.,Mellert, W.,Deckardt, K.,Gembardt, C.,Hildebrand, B.,Parod, R. J.,McCarthy, T. J.,Griffiths, J. C. (1999). 90-day subchronic toxicity study in rats and mice fed N-methylpyrrolidone (NMP) including neurotoxicity evaluation in rats Drug and Chemical Toxicology, 22(3), 455-480** **HERO ID: 3539912**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance identified by name and CASRN.	High	1	2	2
	2. Test Substance Source	The source was identified.	Medium	2	1	2
	3. Test Substance Purity	The reported purity was such that effects likely due to test substance.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Negative control animals were included.	High	1	2	2
	5. Positive Controls	Positive controls not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Animals allocated by computerized stratified randomization.	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Limited preparation details were reported, but no storage information was presented. Stability of the test substance in the diet was established.	High	1	1	1
	8. Consistency of Exposure Administration	Exposures were administered consistently.	Medium	2	1	2
	9. Reporting of Doses/Concentrations	Doses were reported.	High	1	2	2
	10. Exposure Frequency and Duration	Frequency and duration were reported.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups and spacing were reported and justified.	High	1	1	1
	12. Exposure Route and Method	The route and method were reported.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The source, species, strain, sex, age, initial body weight, and health status were reported.	High	1	2	2

Study reference:	**Malley, L. A.,Kennedy, G. L.,Elliott, G. S.,Slone, T. W.,Mellert, W.,Deckardt, K.,Gembardt, C.,Hildebrand, B.,Parod, R. J.,McCarthy, T. J.,Griffiths, J. C. (1999). 90-day subchronic toxicity study in rats and mice fed N-methylpyrrolidone (NMP) including neurotoxicity evaluation in rats Drug and Chemical Toxicology, 22(3), 455-480** **HERO ID: 3539912**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	14. Adequacy and Consistency of Animal Husbandry Conditions	All conditions except for room air changes were reported.	Medium	2	1	2
	15. Number per Group	the number of animals per group was appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Outcome assessment methodology was reported.	High	1	2	2
	17. Consistency of Outcome Assessment	Outcomes were assessed consistently.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate.	High	1	1	1
	19. Blinding of Assessors	Experimenters conducting the FOB evaluations were blind with respect to the exposure group of each animal.	Medium	2	1	2
	20. Negative Control Response	Negative control responses were appropriate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables were reported.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	No health outcomes unrelated to exposure were observed.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were appropriate.	High	1	1	1
	24. Reporting of Data	Data were reported.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**30**	**37**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.2174**	**Overall Score: Nearest *:**	**1.2**

Study reference:	**Malley, L. A.,Kennedy, G. L.,Elliott, G. S.,Slone, T. W.,Mellert, W.,Deckardt, K.,Gembardt, C.,Hildebrand, B.,Parod, R. J.,McCarthy, T. J.,Griffiths, J. C. (1999). 90-day subchronic toxicity study in rats and mice fed N-methylpyrrolidone (NMP) including neurotoxicity evaluation in rats Drug and Chemical Toxicology, 22(3), 455-480** **HERO ID: 3539912**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
		Overall Quality Level:		**High**		

2.3. Animal toxicity evaluation results of Becci et al 1983 for a 13-week diet study in dogs on body weight, hematological, and immune outcomes

Study reference:	**Becci, P. J., Gephart, L. A., Koschier, F. J., Johnson, W. D., Burnette, L. W. (1983). Subchronic feeding study in beagle dogs of N-methylpyrrolidone Journal of Applied Toxicology, 3(2), 83-86** **HERO ID: 3539728**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	test substance identified by name and CASRN.	High	1	2	2
	2. Test Substance Source	source identified.	Medium	2	1	2
	3. Test Substance Purity	The purity of the test substance was reported (99.9%).	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Negative control animals were included.	High	1	2	2
	5. Positive Controls	Positive controls were not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Allocation method was not reported.	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Preparation was reported, but storage and analysis was not.	Low	3	1	3
	8. Consistency of Exposure Administration	Exposures were administered consistently.	High	1	1	1
	9. Reporting of Doses/Concentrations	Doses were reported.	High	1	2	2
	10. Exposure Frequency and Duration	Frequency and duration were reported.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of groups and spacing were reported, but not justified.	Medium	2	1	2
	12. Exposure Route and Method	The route and method were reported.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The source, species, strain, and age were reported. Health status and initial body weight were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Humidity, housing, and room air changes were not reported.	Medium	2	1	2

Study reference:	Becci, P. J., Gephart, L. A., Koschier, F. J., Johnson, W. D., Burnette, L. W. (1983). Subchronic feeding study in beagle dogs of N-methylpyrrolidone Journal of Applied Toxicology, 3(2), 83-86 HERO ID: 3539728					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	15. Number per Group	The number of animals was appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Outcome assessment methodology was reported and appropriate.	High	1	2	2
	17. Consistency of Outcome Assessment	Outcomes were assessed consistently.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate.	High	1	1	1
	19. Blinding of Assessors	Blinding was not required.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses were appropriate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables were observed.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	No health outcomes unrelated to exposure were observed.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were reported and appropriate	High	1	1	1
	24. Reporting of Data	Data were reported.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**28**	**38**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.3571**	**Overall Score: Nearest *:**	**1.4**
		Overall Quality Level:		**High**		

3. Cancer Studies

3.1. Animal toxicity evaluation results of E.I. Dupont De Nemours Co. 1982 for a 2-year inhalation study in rats on renal and cancer outcomes

Study reference:	**E. I. Dupont De Nemours Co, (1982). 2-YEAR INHALATION STUDY WITH N-METHYL-2-PYRROLIDONE IN RATS (FINAL) WITH COVER LETTER DATED 083090** **HERO ID: 4214102**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance identified by name.	Medium	2	2	4
	2. Test Substance Source	Sponsor identified as source of test substance.	Low	3	1	3
	3. Test Substance Purity	Purity such that effects likely due to the test substance. Impurities were identified.	Medium	2	1	2
Test Design	4. Negative and Vehicle Controls	Negative controls were used.	High	1	2	2
	5. Positive Controls	Positive controls were not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Selective allocation was used so that the mean body weights were equal across groups and sex.	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Generation of vapors were reported and appropriate; storage of test substance was not reported.	Medium	2	1	2
	8. Consistency of Exposure Administration	Exposure periods were occasionally shorter than 6 hours or missed entirely because of mechanical problems.	Low	3	1	3
	9. Reporting of Doses/Concentrations	Concentrations were presented without ambiguity.	High	1	2	2
	10. Exposure Frequency and Duration	Frequency and duration were reported and appropriate.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups and dose spacing were appropriate but not justified.	Medium	2	1	2
	12. Exposure Route and Method	Deficiencies in reporting of aerosol formation.	High	1	1	1

Study reference:	E. I. Dupont De Nemours Co, (1982). 2-YEAR INHALATION STUDY WITH N-METHYL-2-PYRROLIDONE IN RATS (FINAL) WITH COVER LETTER DATED 083090 HERO ID: 4214102					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Organism	13. Test Animal Characteristics	The source, species, strain, age, health status, sex, and body weight at start of test were reported.	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	All husbandry conditions were reported.	High	1	1	1
	15. Number per Group	The number of animals per group was appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Breathing rate was not reported.	Low	3	2	6
	17. Consistency of Outcome Assessment	Outcome assessments were consistent.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate for the endpoints examined.	High	1	1	1
	19. Blinding of Assessors	Blinding was not required.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses were appropriate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	One male control rat was placed in the female group. Several rats in the low-exposure group escaped and mated. Several rats escaped and were never recaptured.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	Three female rats were impregnated by a male rat, gave birth, and were continued in the study. One low-exposure female was impregnated, gave birth, and was continued on the test.	Low	3	1	3
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were described. It does not appear that incidence data were analyzed.	Low	3	1	3

Study reference:	E. I. Dupont De Nemours Co, (1982). 2-YEAR INHALATION STUDY WITH N-METHYL-2-PYRROLIDONE IN RATS (FINAL) WITH COVER LETTER DATED 083090 HERO ID: 4214102					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	24. Reporting of Data	Data were presented for all outcomes.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**52**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.7931**	**Overall Score: Nearest *:**	**1.8**
		Overall Quality Level:		**Medium**		

N-Methylpyrrolidone

3.2. Animal toxicity evaluation results of Malley et al 2001 for an oral cancer rats and mice study on cancer, hepatic, and renal outcomes

Study reference:	**Malley, L. A., Kennedy, G. L., Elliott, G. S., Slone, T. W., Mellert, W., Deckardt, K., Kuttler, K., Hildebrand, B., Banton, M. I., Parod, R. J., Griffiths, J. C. (2001). Chronic toxicity and oncogenicity of N-methylpyrrolidone (NMP) in rats and mice by dietary administration Drug and Chemical Toxicology, 24(4), 315-338** **HERO ID: 3539913**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance identified by name and CASRN.	High	1	2	2
	2. Test Substance Source	Source identified by name.	Medium	2	1	2
	3. Test Substance Purity	The reported purity was such that effects are likely due to the test substance.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Negative control animals were included.	High	1	2	2
	5. Positive Controls	Positive controls were not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	allocation was by computerized stratified randomization.	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Preparation details were limited, but stability, homogeneity, and concentration analysis were conducted.	Medium	2	1	2
	8. Consistency of Exposure Administration	Exposures were administered consistently.	High	1	1	1
	9. Reporting of Doses/Concentrations	Doses were reported.	High	1	2	2
	10. Exposure Frequency and Duration	Frequency and duration information were reported.	Medium	2	1	2
	11. Number of Exposure Groups and Dose Spacing	The number of groups and spacing were reported and justified.	High	1	1	1
	12. Exposure Route and Method	Route and method were appropriate.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The source, species, strain, age, initial body weight, and health status were reported.	High	1	2	2

Study reference:	**Malley, L. A., Kennedy, G. L., Elliott, G. S., Slone, T. W., Mellert, W., Deckardt, K., Kuttler, K., Hildebrand, B., Banton, M. I., Parod, R. J., Griffiths, J. C. (2001). Chronic toxicity and oncogenicity of N-methylpyrrolidone (NMP) in rats and mice by dietary administration Drug and Chemical Toxicology, 24(4), 315-338** **HERO ID: 3539913**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	14. Adequacy and Consistency of Animal Husbandry Conditions	All conditions were reported except for room air changes.	Medium	2	1	2
	15. Number per Group	The number of animals was appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Outcome assessment methodology was appropriate.	High	1	2	2
	17. Consistency of Outcome Assessment	Outcomes were administered consistently.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate.	High	1	1	1
	19. Blinding of Assessors	Blinding was not required.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses were appropriate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables were reported.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	No health outcomes unrelated to exposures were reported.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were reported and appropriate.	High	1	1	1
	24. Reporting of Data	Data were reported.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**36**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.2273**	**Overall Score: Nearest *:**	**1.2**
		Overall Quality Level:		**High**		

3.3. Animal toxicity evaluation results of N-Methylpyrrolidone Producers Group 1997 for a 2-year cancer bioassay study

Study reference:	**N-Methylpyrrolidone Producers Group, Inc (1997). FINAL REPORT, ONCOGENICITY STUDY WITH N-METHYLPYRROLIDONE (NMP) TWO-YEAR FEEDING STUDY IN SPRAGUE DAWLEY RATS, WITH COVER LETTER DATED 5/22/1998** **HERO ID: 4214107**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Identified by structure, nomenclature, CASRN.	High	1	2	2
	2. Test Substance Source	Source and production date provided	High	1	1	1
	3. Test Substance Purity	Purity such that effects due to test substance.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Concurrent negative controls were used	High	1	2	2
	5. Positive Controls	Positive control animals were not required	Not Rated	NA	NA	NA
	6. Randomized Allocation	Computerized stratified randomization used to ensure no body weight differences among the groups	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Preparation and storage were appropriate based on stability analysis	High	1	1	1
	8. Consistency of Exposure Administration	Diets administered consistently across groups	High	1	1	1
	9. Reporting of Doses/Concentrations	Food intake and body weight were monitored in order to calculate daily intakes. Concentrations were analyzed in the diet	High	1	2	2
	10. Exposure Frequency and Duration	Diets were provided for "approximately 24 months" and were inferred to have been available ad libitum	Medium	2	1	2
	11. Number of Exposure Groups and Dose Spacing	The number of groups and spacing were based on previous repeated dose studies	High	1	1	1
	12. Exposure Route and Method	The route and methods were suitable for the test substance	High	1	1	1
Test Organism	13. Test Animal Characteristics	All characteristics were reported	High	1	2	2

Study reference:	N-Methylpyrrolidone Producers Group, Inc (1997). FINAL REPORT, ONCOGENICITY STUDY WITH N-METHYLPYRROLIDONE (NMP) TWO-YEAR FEEDING STUDY IN SPRAGUE DAWLEY RATS, WITH COVER LETTER DATED 5/22/1998 HERO ID: 4214107					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	14. Adequacy and Consistency of Animal Husbandry Conditions	All conditions were reported	High	1	1	1
	15. Number per Group	The number of animals/group was adequate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Outcomes methodology was reported and sensitive for outcome(s) of interest	High	1	2	2
	17. Consistency of Outcome Assessment	Outcomes were assessed consistently	High	1	1	1
	18. Sampling Adequacy	Sampling for outcomes was adequate	High	1	1	1
	19. Blinding of Assessors	Blinding was not reported for peer-review evaluation of histopathological findings, but this is not expected to impact on the results.	Medium	2	1	2
	20. Negative Control Response	The negative controls responded appropriately	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables were reported	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	No health outcomes unrelated to exposure were found.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were appropriate for the outcomes	High	1	1	1
	24. Reporting of Data	All outcomes were reported	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**30**	**33**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.1000**	**Overall Score: Nearest *:**	**1.1**

Study reference:	N-Methylpyrrolidone Producers Group, Inc (1997). FINAL REPORT, ONCOGENICITY STUDY WITH N-METHYLPYRROLIDONE (NMP) TWO-YEAR FEEDING STUDY IN SPRAGUE DAWLEY RATS, WITH COVER LETTER DATED 5/22/1998 HERO ID: 4214107					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
		Overall Quality Level:		**High**		

4. Reproductive/Developmental Toxicity Studies

4.1. Animal toxicity evaluation results of Becci et al 1982 for a dermal, developmental study in rats (rf and final-study report in 4214125) on growth (early life) and development outcomes

Study reference:	**Becci, P. J.,Knickerbocker, M. J.,Reagan, E. L.,Parent, R. A.,Burnette, L. W. (1982). Teratogenicity study of N-methylpyrrolidone after dermal application to Sprague-Dawley rats Fundamental and Applied Toxicology, 2(2), 73-76** **HERO ID: 3539729**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance was identified by name.	Medium	2	2	4
	2. Test Substance Source	The sponsor (GAF Corp) was identified as the source.	Low	3	1	3
	3. Test Substance Purity	The purity (99.9%) was such that effects likely due to the test substance.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Concurrent negative controls were used in both studies.	High	1	2	2
	5. Positive Controls	Concurrent positive controls were used; however, a similar incidence was observed for incomplete ossification between negative and positive controls.	Low	3	1	3
	6. Randomized Allocation	Method of allocation not reported.	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Authors note that the positive control solutions were prepared fresh daily, but preparation and storage of the test material was not reported.	Low	3	1	3
	8. Consistency of Exposure Administration	Test material was rubbed into skin and the test site remained uncovered. It is unclear whether doses were administered consistently.	Low	3	1	3
	9. Reporting of Doses/Concentrations	Doses were reported.	High	1	2	2

Study reference:	**Becci, P. J.,Knickerbocker, M. J.,Reagan, E. L.,Parent, R. A.,Burnette, L. W. (1982). Teratogenicity study of N-methylpyrrolidone after dermal application to Sprague-Dawley rats Fundamental and Applied Toxicology, 2(2), 73-76** **HERO ID: 3539729**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Exposure Frequency and Duration	Frequency and duration were adequate.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	Exposure groups (n) was adequate; however, doses and spacing were not adequately justified (i.e., no effects observed at 500 mg/kg in range finding study).	Low	3	1	3
	12. Exposure Route and Method	Route and method were reported.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The source, species, strain, and sex were reported. Age, initial body weight, and health status were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Housing, temperature, and lighting were reported. Humidity and air changes were not reported.	Medium	2	1	2
	15. Number per Group	The number of animals was appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Treatment through organogenesis (GD 16 in rats) is recommended for teratology assessments.	Medium	2	2	4
	17. Consistency of Outcome Assessment	Based on examination of urine, only 1 animal treated at 75 mg/kg showed evidence of exposure.	Low	3	1	3
	18. Sampling Adequacy	Sampling was adequate.	High	1	1	1
	19. Blinding of Assessors	Blinding was not required.	Not Rated	NA	NA	NA
	20. Negative Control Response	A similar incidence was observed for incomplete ossification between negative and positive controls	Low	3	1	3

Study reference:	**Becci, P. J.,Knickerbocker, M. J.,Reagan, E. L.,Parent, R. A.,Burnette, L. W. (1982). Teratogenicity study of N-methylpyrrolidone after dermal application to Sprague-Dawley rats Fundamental and Applied Toxicology, 2(2), 73-76** **HERO ID: 3539729**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables were reported.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	No health effects unrelated to exposure were reported.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were described and appropriate.	High	1	1	1
	24. Reporting of Data	Data were reported for all outcomes.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**53**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.8276**	**Overall Score: Nearest *:**	1.8
		Overall Quality Level:		**Medium**		

4.2. Animal toxicity evaluation results of Ciba-Geigy 1987 for an oral developmental rat study on growth (early life) and development outcomes

Study reference:	**Ciba-Geigy, Corp (1987). LETTER FROM CIBA-GEIGY CORPORATION TO USEPA REGARDING INFORMATION ON THE ENCLOSED REPORTS CONCERNING N-METHYLPYRROLIDONE WITH ATTACHMENTS** **HERO ID: 4214093**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	See footnote at end of page.[1]	High	1	2	2
	2. Test Substance Source	The source was not identified.	Low	3	1	3
	3. Test Substance Purity	The purity was not reported; stated to be double distilled.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	No information on the age/weight of negative (untreated) control animals was provided.	Medium	2	2	4
	5. Positive Controls	Positive controls were not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Method of randomization not reported.	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Information on storage/stability was not provided.	Low	3	1	3
	8. Consistency of Exposure Administration	See footnote at bottom of page[1]	High	1	1	1
	9. Reporting of Doses/Concentrations	Doses were reported as (mm^3/kg); however, specific information needed to confirm dose calculations (purity, body weight) was not provided.	Low	3	2	6
	10. Exposure Frequency and Duration	Frequency and duration were reported; however, the duration of exposure was inadequate based on OECD 422 standards.	Low	3	1	3
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups and dose spacing were inadequate based on OECD 422 standards.	Low	3	1	3

[1] Metrics that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	Ciba-Geigy, Corp (1987). LETTER FROM CIBA-GEIGY CORPORATION TO USEPA REGARDING INFORMATION ON THE ENCLOSED REPORTS CONCERNING N-METHYLPYRROLIDONE WITH ATTACHMENTS HERO ID: 4214093					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	12. Exposure Route and Method	Translated summaries provided for i.p., oral and inhalation exposures. Limited information provided for generation of inhalation concentrations is.	Low	3	1	3
Test Organism	13. Test Animal Characteristics	The source, species, strain, and sex were reported. Age, initial body weight, and health status were not reported.	Low	3	2	6
	14. Adequacy and Consistency of Animal Husbandry Conditions	Housing, feed, water, temperature, and humidity were reported. Lighting and number of room air changes were not reported.	Medium	2	1	2
	15. Number per Group	The number of animals was adequate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Description of outcome assessment methodology is inadequate.	Low	3	2	6
	17. Consistency of Outcome Assessment	It is difficult to discern whether outcomes were assessed consistently based on translated text.	Low	3	1	3
	18. Sampling Adequacy	Sampling was adequate.	Medium	2	1	2
	19. Blinding of Assessors	Blinding not required.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses were not appropriate. The total malformation rate in untreated controls (2.6%) exceeded the spontaneous value reported in historical controls (1.7%)	Low	3	1	3
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables were reported.	High	1	2	2

Study reference:	Ciba-Geigy, Corp (1987). LETTER FROM CIBA-GEIGY CORPORATION TO USEPA REGARDING INFORMATION ON THE ENCLOSED REPORTS CONCERNING N-METHYLPYRROLIDONE WITH ATTACHMENTS HERO ID: 4214093					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Health Outcomes Unrelated to Exposure	No information provided regarding health outcomes unrelated to exposure were reported.	Low	3	1	3
Data Presentation and Analysis	23. Statistical Methods	Statistical analysis was not conducted, but data were available to conduct analysis.	Low	3	1	3
	24. Reporting of Data	Maternal body weights were not reported. Litter data were not presented.	Low	3	2	6
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**71**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**2.4423**	**Overall Score: Nearest *:**	**2.4**
		Overall Quality Level:		**Low**		

4.3. Animal toxicity evaluation results of E. I. Dupont De Nemours 1979 for a developmental range-finding: rats study on growth (early life) and development outcomes

Study reference:	**E. I. Dupont De Nemours Co., (1979). INITIAL SUBMISSION: TERATOLOGIC DOSE RANGE-FINDING STUDY W/ N-METHYLPYRROLIDONE IN SPRAGUE DAWLEY RATS WITH COVER LETTER DATED 09/01/92** **HERO ID: 3564297**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance identified by name and lot number.	Medium	2	2	4
	2. Test Substance Source	The sponsor was identified as the source of the test substance.	Low	3	1	3
	3. Test Substance Purity	Test substance purity was reported	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Concurrent negative controls were included.	High	1	2	2
	5. Positive Controls	Concurrent positive controls were used; however, a similar incidence of incomplete ossification was observed in positive and negative controls.	Low	3	1	3
	6. Randomized Allocation	A random number assignment sheet was used.	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Preparation and storage of test material was not provided. However, it was reported that the positive control agent was prepared fresh daily.	Low	3	1	3
	8. Consistency of Exposure Administration	Test material was rubbed into skin and the test site remained uncovered; therefore, it is unclear whether doses were administered consistently.	Low	3	1	3
	9. Reporting of Doses/Concentrations	Doses were reported.	High	1	2	2
	10. Exposure Frequency and Duration	Duration and frequency were inadequate for this type of study.	Low	3	1	3

Study reference:	E. I. Dupont De Nemours Co., (1979). INITIAL SUBMISSION: TERATOLOGIC DOSE RANGE-FINDING STUDY W/ N-METHYLPYRROLIDONE IN SPRAGUE DAWLEY RATS WITH COVER LETTER DATED 09/01/92 HERO ID: 3564297					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	11. Number of Exposure Groups and Dose Spacing	The number of animals in each group was adequate; however, dose selection and spacing were not justified/inadequate. No effects were observed in animals treated at 500 mg/kg in range finding study).	Low	3	1	3
	12. Exposure Route and Method	Exposure route and method were reported.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The source, species, strain, initial body weight, sex, and sexual state were reported. The health status and specific age of the parents was not reported, but they were sexually mature.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Housing, feed and water were reported. Temperature, humidity, lighting, and air changes were not reported.	Medium	2	1	2
	15. Number per Group	The number of animals was acceptable for a range-finding study.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Treatment did not extend through the entire period of organogenesis.	Medium	2	2	4
	17. Consistency of Outcome Assessment	Based on an examination of urine, only 1 animal treated at 75 mg/kg showed evidence of exposure.	Low	3	1	3
	18. Sampling Adequacy	Sampling was adequate.	High	1	1	1
	19. Blinding of Assessors	Blinding was not required in this study.	Not Rated	NA	NA	NA
	20. Negative Control Response	Similar incidence of incomplete ossification observed between negative and positive controls.	Low	3	1	3

Study reference:	E. I. Dupont De Nemours Co., (1979). INITIAL SUBMISSION: TERATOLOGIC DOSE RANGE-FINDING STUDY W/ N-METHYLPYRROLIDONE IN SPRAGUE DAWLEY RATS WITH COVER LETTER DATED 09/01/92 HERO ID: 3564297					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables in test design and procedures were noted.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	No health outcomes unrelated to exposures were reported.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were reported and appropriate.	High	1	1	1
	24. Reporting of Data	Data presentation for all outcomes was adequate.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**30**	**54**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.8**	**Overall Score: Nearest *:**	**1.8**
		Overall Quality Level:		**Medium**		

4.4. Animal toxicity evaluation results of Intl Specialty 1979 for dermal developmental, offspring and maternal effects study on growth (early life) and development outcomes

Study reference:	**Intl Specialty, Prods (1979). INITIAL SUBMISSION: TERATOLOGICAL DOSE RANGE-FINDING STUDY WITH N-METHYLPYRROLIDONE IN SPRAGUE-DAWLEY RATS (FINAL REPORT) WITH ATTACHMENTS AND COVER LETTER DATED 022792** **HERO ID: 4214125**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance identified by name.	Medium	2	2	4
	2. Test Substance Source	Sponsor (GAF Corp) was identified as the source of the test substance.	Low	3	1	3
	3. Test Substance Purity	Purity such that effects due to test substance.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Concurrent negative controls were used.	High	1	2	2
	5. Positive Controls	See footnote at end of page.[1]	High	1	1	1
	6. Randomized Allocation	Animals allocated by random number assignment sheet.	Medium	2	1	2
Exposure Characteriz[1]ation	7. Preparation and Storage of Test Substance	Preparation and storage were not reported.	Low	3	1	3
	8. Consistency of Exposure Administration	Test material was rubbed into the skin. Dosing volume, diluent or dilution factor were not described. It is unclear whether doses were administered consistently.	Low	3	1	3
	9. Reporting of Doses/Concentrations	Doses were reported.	High	1	2	2
	10. Exposure Frequency and Duration	Exposure duration and frequency were reported.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of groups and dose spacing were reported and justified.	High	1	1	1

[1] Metric that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	Intl Specialty, Prods (1979). INITIAL SUBMISSION: TERATOLOGICAL DOSE RANGE-FINDING STUDY WITH N-METHYLPYRROLIDONE IN SPRAGUE-DAWLEY RATS (FINAL REPORT) WITH ATTACHMENTS AND COVER LETTER DATED 022792 HERO ID: 4214125					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	12. Exposure Route and Method	The route and method of exposure were appropriate.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The source, strain, sexual state, sex, and initial body weight were reported. Health status and specific numeric age were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Temperature, lighting, and humidity were not reported.	Medium	2	1	2
	15. Number per Group	The number of animals per group was appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Treatment did not extend throughout the period of organogenesis.	Medium	2	2	4
	17. Consistency of Outcome Assessment	Outcomes were assessed consistently.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate for the outcomes of interest.	High	1	1	1
	19. Blinding of Assessors	Blinding was not required.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses were appropriate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables in test design and procedures were noted.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	No health outcomes unrelated to exposures were observed.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were described and appropriate.	High	1	1	1
	24. Reporting of Data	Data were presented for all outcomes.	High	1	2	2
		Sum of scores:			**29**	**44**

Study reference:	Intl Specialty, Prods (1979). INITIAL SUBMISSION: TERATOLOGICAL DOSE RANGE-FINDING STUDY WITH N-METHYLPYRROLIDONE IN SPRAGUE-DAWLEY RATS (FINAL REPORT) WITH ATTACHMENTS AND COVER LETTER DATED 022792 HERO ID: 4214125					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:**		**1.5172**	**Overall Score: Nearest *:**	**1.5**
		Overall Quality Level:		**High**		

4.5. Animal toxicity evaluation results of Exxon Biomedical 1991 for a multigeneration reproductive toxicity study on rats – reproductive, growth (early life) and developmental outcomes

Study reference:	**Exxon Biomedical (1991). Multigeneration Rat Reproduction Study with N-Methylpyrrolidone, Project Number 236535** **HERO ID: 3809420**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	The test substance was identified as N-methylpyrrolidone by name in the study title (CASRN not provided). The test substance is referred to as MRD-89-365 throughout the study report.	High	1	2	2
	2. Test Substance Source	The study report indicates that the synthesis, fabrication, and/or derivation of the test substance were the responsibility of the sponsor (GAF Corporation). The batch number is identified (I), but the manufacturer (if applicable) was not explicitly identified. Although the materials and methods reference a certificate of analysis, it was not included in the study report (i.e., not found in an appendix).	Medium	2	1	2
	3. Test Substance Purity	The study report indicates that the test substance was assumed 100% pure for the purposes of dosing. Purity was not reported explicitly, but given other information (i.e., analyses of the test substance in feed mixtures), this was not expected to substantially impact the study results.	Medium	2	1	2

Study reference:	**Exxon Biomedical (1991). Multigeneration Rat Reproduction Study with N-Methylpyrrolidone, Project Number 236535** **HERO ID: 3809420**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Design	4. Negative and Vehicle Controls	The study authors reported using an appropriate concurrent negative control group (conditions the same except for treatment). Controls were given the same rodent chow as treated animals (minus addition of the test substance).	High	1	2	2
	5. Positive Controls	Positive control not indicated by study type.	Not Rated	NA	NA	NA
	6. Randomized Allocation	The study report indicates that rats (F0 generation) were selected using a computer-generated sorting program so that weight variations were within 20% of the group mean body weight. Rats were randomly allocated to groups by computer (with an attempt to nearly equalize initial body weights).	High	1	1	1
Exposure Characterization	7. Preparation and Storage of Test Substance	The test substance was thoroughly mixed into the diet; jars containing the feed were replaced at least weekly. Homogeneity, stability, and concentration analyses were performed. Homogeneity samples (top, middle, and bottom for the low- and high-dose groups only) were within 7% of the target values; stability analyses indicated the test substance was stable for at least one month.	High	1	1	1

Study reference:	**Exxon Biomedical (1991). Multigeneration Rat Reproduction Study with N-Methylpyrrolidone, Project Number 236535** **HERO ID: 3809420**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	8. Consistency of Exposure Administration	Details of exposure administration were reported and exposure were administered consistently across groups. All groups of rats were administered the test substance in the diet (offered ad libitum).	High	1	1	1
	9. Reporting of Doses/ Concentrations	Target doses were 0, 50, 160, and 500 mg/kg-day. Concentrations of the test substance in the diet were adjusted during pre-mating, and maintained constant thereafter (i.e., during mating, gestation, and lactation) . Based on measured data, doses were generally within 20% of target levels during premating and gestation. Although no test substance intake information was available during mating, the current guideline indicates that test substance intake data are required except during cohabitation .The study notes that males were dosed at lower than target dose levels during this period (as dosing based on female body weight/food consumption data). Test substance intake was inconsistent during lactation. Doses were higher than target levels from PND 4 on, reaching 2 to 3x target levels by PND 21. In general, body weight and food consumption data were available to enable calculations.	Medium	2	2	4

Study reference:	**Exxon Biomedical (1991). Multigeneration Rat Reproduction Study with N-Methylpyrrolidone, Project Number 236535** **HERO ID: 3809420**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Exposure Frequency and Duration	The exposure frequency and duration were reported and appropriate for the study type/outcomes of interest. Animals were dosed during pre-mating, mating, gestation, lactation, and/or until weaning of the F2b litter.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The target doses were based on data for a previously conducted dose-probe study. The high-dose was sufficient to induce treatment-related effects (i.e., selected doses enable evaluation of dose-response effects). However, the target dose intervals were slightly more than 3-fold (current guideline suggests that for dietary studies, the dose interval should not be more than 3-fold).	High	1	1	1
	12. Exposure Route and Method	The route and method of exposure were reported and were suited to the test substance. Based on homogeneity and stability analyses, the test substance was non-volatile in the diet.	High	1	1	1

Study reference:	**Exxon Biomedical (1991). Multigeneration Rat Reproduction Study with N-Methylpyrrolidone, Project Number 236535** **HERO ID: 3809420**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Organism	13. Test Animal Characteristics	The test animal species, strain, sex, health status, age, and initial body weights were reported. Rats used in the study were obtained from a commercial source. The test species and strain were an appropriate model; the study report indicates that rats have historically been used for multi-generation reproduction studies (rats are the preferred species based on OECD guideline).	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	Husbandry conditions were reported and were generally considered adequate. Some differences in conditions were noted (occasions in which room temperature and/or humidity were out of range), but all dose groups were presumably affected by these deviations, and they are not expected to substantially impact the study results.	Medium	2	1	2
	15. Number per Group	The number of animals/group (30/sex/generation) was reported and was appropriate for the study type (guideline recommendation of no fewer than 20 pregnant females at or near parturition).	High	1	1	1

Study reference:	**Exxon Biomedical (1991). Multigeneration Rat Reproduction Study with N-Methylpyrrolidone, Project Number 236535** **HERO ID: 3809420**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	16. Outcome Assessment Methodology	In general, the outcome assessment methodology addressed/ reported the intended outcomes of interest; reproductive/ developmental parameters were evaluated over the course of two generations. However, several endpoints recommended by current guidelines were not evaluated, including organ weights, estrous cycle parameters (normality), and sperm parameters (motility and morphology) in parental animals.	Medium	2	2	4
	17. Consistency of Outcome Assessment	The timing/methods of outcome assessments were reported and appeared to be consistent across treatment groups.	High	1	1	1
	18. Sampling Adequacy	In general, details regarding sampling were reported. However, it appears that mean fetal body weight data are based on n = number of fetuses (i.e., the litter was not the basis for analysis). Although histopathological examinations were performed for low- and high-dose groups only (which is acceptable as per the current guideline), additional dose groups were examined when histopathological findings were observed at the high dose (e.g., in the ovaries and uterus of female rats).	Medium	2	1	2

Study reference:	Exxon Biomedical (1991). Multigeneration Rat Reproduction Study with N-Methylpyrrolidone, Project Number 236535 HERO ID: 3809420					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	19. Blinding of Assessors	The study report included a quality assurance statement with respect to histopathology examinations, indicating that evaluations were performed according to standard operating procedures, audited., and based on good laboratory practice. Other endpoints evaluated in the study were not subjective.	High	1	1	1
	20. Negative Control Response	The biological responses of the negative control group were adequate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	There were no significant differences among study groups with respect to initial body weights or food consumption rates.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	There were no outcomes reported unrelated to exposure. There were only a few unscheduled deaths (which were considered incidental). Effects observed in histopathological examinations that were not treatment-related were considered spontaneous (not attributed to a cause like infection).	High	1	1	1

Study reference:	**Exxon Biomedical (1991). Multigeneration Rat Reproduction Study with N-Methylpyrrolidone, Project Number 236535** **HERO ID: 3809420**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Data Presentation and Analysis	23. Statistical Methods	The body of the study report indicates that mean body weights and food consumption were analyzed statistically for significant differences. However, the discussion references other "statistically significant effects" (e.g., on fertility and fecundity indices); these are not marked as statistically significant in the corresponding data tables. While sufficient data (n, mean, and measure of variance) are provided in most cases, some of these data would have to be obtained from data tables on individual animals. Appendix AQ indicates that most data were not analyzed statistically (including fertility indices).	Low	3	1	3

Study reference:	**Exxon Biomedical (1991). Multigeneration Rat Reproduction Study with N-Methylpyrrolidone, Project Number 236535** **HERO ID: 3809420**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	24. Reporting of Data	Data for treatment-related findings were reported for most, but not all, outcomes appropriately. For example, reproductive indices were reported, but the numbers used for calculating these indices were not explicitly provided. However, these data could be pieced together by evaluating individual reproduction data (available in appendices). Data for gestation length are also available based on individual data only. Similarly, necropsy data were not presented in a summary table, but individual data were available.	Medium	2	2	4
High: >=1 and <1.7 **Medium: >=1.7 and <2.3** **Low: >=2.3 and <=3**		**Sum of scores:**			**30**	**42**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.400**	**Overall Score: Nearest *:**	1.4
		Overall Quality Level:		**High**		

4.6. Animal toxicity evaluation results of Exxon 1992 for a developmental toxicity study in rats on growth (early life) and development outcomes

Study reference:	**Exxon (1992). INITIAL SUBMISSION: DEVELOPMENTAL TOXICITY STUDY IN RATS WITH N-METHYLPYRROLIDONE (DRAFT REPORT) WITH ATTACHMENTS AND COVER LETTER DATED 041092** **HERO ID: 3563347 and 4214126**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance identified by name. Characterization and analysis of the test article were reported to be documented by the sponsor, but no details were provided.	Medium	2	2	4
	2. Test Substance Source	The batch number was provided. The source was of the test substance was not provided but reported as sponsor.	Medium	2	1	2
	3. Test Substance Purity	The purity was assumed to be 100%, however no data was provided for support.	Medium	2	1	2
Test Design	4. Negative and Vehicle Controls	A concurrent vehicle control was included.	High	1	2	2
	5. Positive Controls	Positive controls were not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Method of allocation was based on confirmed mating.	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Test substance preparation and storage were reported. Stability and concentration were reported.	High	1	1	1
	8. Consistency of Exposure Administration	Doses were administered consistently.	High	1	1	1
	9. Reporting of Doses/Concentrations	Doses were reported.	High	1	2	2
	10. Exposure Frequency and Duration	Duration and frequency were reported.	High	1	1	1

Study reference:	**Exxon (1992). INITIAL SUBMISSION: DEVELOPMENTAL TOXICITY STUDY IN RATS WITH N-METHYLPYRROLIDONE (DRAFT REPORT) WITH ATTACHMENTS AND COVER LETTER DATED 041092** **HERO ID: 3563347 and 4214126**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	11. Number of Exposure Groups and Dose Spacing	The number of groups and spacing were not justified but were sufficient to show results relevant to the outcome of interest.	Medium	2	1	2
	12. Exposure Route and Method	The exposure route and method were appropriate.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The source, species, strain, sex, health status, and initial body weight were reported.	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	All husbandry conditions were reported.	High	1	1	1
	15. Number per Group	The number of animals per group was appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Outcome assessment methodology was described and appropriate.	High	1	2	2
	17. Consistency of Outcome Assessment	Outcome assessment was consistent.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate.	High	1	1	1
	19. Blinding of Assessors	Blinding not required in this assay.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses were appropriate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Distribution by mating confirmation resulted in 4 non-pregnant control animals, but there were a sufficient number of offspring available for comparison.	Medium	2	2	4
	22. Health Outcomes Unrelated to Exposure	No health outcomes unrelated to exposure were observed.	High	1	1	1

Study reference:	Exxon (1992). INITIAL SUBMISSION: DEVELOPMENTAL TOXICITY STUDY IN RATS WITH N-METHYLPYRROLIDONE (DRAFT REPORT) WITH ATTACHMENTS AND COVER LETTER DATED 041092 HERO ID: 3563347 and 4214126					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were well described and appropriate.	High	1	1	1
	24. Reporting of Data	Data were reported for all outcomes.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**37**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.2759**	**Overall Score: Nearest *:**	**1.3**
		Overall Quality Level:		**High**		

4.7. Animal toxicity evaluation results of Lee et al 1987 for an inhalation developmental study on growth (early life) and development outcomes

Study reference:	**Lee, K. P.,Chromey, N. C.,Culik, R.,Barnes, J. R.,Schneider, P. W. (1987). Toxicity of N-methyl-2-pyrrolidone (NMP): teratogenic, subchronic, and two-year inhalation studies Fundamental and Applied Toxicology, 9(2), 222-235** **HERO ID: 3539878**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Chemical structure, established nomenclature, and physiochemical properties were reported	High	1	2	2
	2. Test Substance Source	The source was not reported. However, the concentration of exposures were measured by IR spectrometry and gas chromatography.	Medium	2	1	2
	3. Test Substance Purity	The compound was stated to be 100% pure without support for the statement. The concentration of exposures were measured by IR spectrometry and gas chromatography. Thus effects are likely due to the test substance.	Medium	2	1	2
Test Design	4. Negative and Vehicle Controls	A concurrent control group was included	High	1	2	2
	5. Positive Controls	Positive controls not required	Not Rated	NA	NA	NA

Study reference:	**Lee, K. P.,Chromey, N. C.,Culik, R.,Barnes, J. R.,Schneider, P. W. (1987). Toxicity of N-methyl-2-pyrrolidone (NMP): teratogenic, subchronic, and two-year inhalation studies Fundamental and Applied Toxicology, 9(2), 222-235** **HERO ID: 3539878**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	6. Randomized Allocation	Pregnant females were randomly assigned. However, the article states, "In the experiment for teratogenicity, the pregnant female rats were assigned at random into the three groups, but random distribution was not obtained. Five of twenty-five females in the 0.1 mg/liter exposure group were not impregnated. Two of twenty pregnant females had only four and one corpora lutea, respectively, and one implantation each. If these two females were removed from the group, the calculated mean value of parameters measuring the reproduction capability would be similar to those of the control group." The NOAEC was 0.36 mg/L.	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Aerosol generation system was described and appropriate.	High	1	1	1
	8. Consistency of Exposure Administration	Exposures were consistent across groups	High	1	1	1
	9. Reporting of Doses/Concentrations	The particle size distribution was not determined and there was uncertainty about whether analytical or nominal concentration was reported.	Low	3	2	6
	10. Exposure Frequency and Duration	Exposed GD6-15 for 6 h/day	High	1	1	1

Study reference:	**Lee, K. P.,Chromey, N. C.,Culik, R.,Barnes, J. R.,Schneider, P. W. (1987). Toxicity of N-methyl-2-pyrrolidone (NMP): teratogenic, subchronic, and two-year inhalation studies Fundamental and Applied Toxicology, 9(2), 222-235** **HERO ID: 3539878**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	11. Number of Exposure Groups and Dose Spacing	Rationale was not provided, but very little impact on results. Only 2 doses were used. Exposures were not high enough to cause toxicity in females or fetuses.	Medium	2	1	2
	12. Exposure Route and Method	Dynamic chambers were used	High	1	1	1
Test Organism	13. Test Animal Characteristics	Age and overall health status were not reported	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Husbandry was not adequately reported.	Low	3	1	3
	15. Number per Group	The number of animals/group was sufficient for outcome analysis	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	The outcomes of interest were addressed by the methodology	High	1	2	2
	17. Consistency of Outcome Assessment	Outcomes were assessed consistently.	High	1	1	1
	18. Sampling Adequacy	Adequate sampling for the outcomes of interest was conducted	High	1	1	1
	19. Blinding of Assessors	Subjective outcomes were not assessed	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative controls responded appropriately	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables were reported. However, NMP is an irritant. Breathing rates and body temperature measurements were not made to rule our reflex bradypnea.	Medium	2	2	4

Study reference:	Lee, K. P.,Chromey, N. C.,Culik, R.,Barnes, J. R.,Schneider, P. W. (1987). Toxicity of N-methyl-2-pyrrolidone (NMP): teratogenic, subchronic, and two-year inhalation studies Fundamental and Applied Toxicology, 9(2), 222-235 HERO ID: 3539878					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Health Outcomes Unrelated to Exposure	The article states "In the experiment for teratogenicity, the pregnant female rats were assigned at random into the three groups, but random distribution was not obtained. Five of twenty-five females in the 0.1 mg/liter exposure group were not impregnated. Two of twenty pregnant females had only four and one corpora lutea, respectively, and one implantation each. If these two females were removed from the group, the calculated mean value of parameters measuring the reproduction capability would be similar to those of the control group." The NOAEC was 0.36 mg/L.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	The described statistical methods were appropriate	High	1	1	1
	24. Reporting of Data	Data were reported for outcomes	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	44
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		1.517	**Overall Score: Nearest *:**	1.5
		Overall Quality Level:		**High**		

4.8. Animal toxicity evaluation results of Saillenfait et al 2002 for an oral developmental rat and maternal effects study on growth (early life), development, and reproductive outcomes

Study reference:	**Saillenfait, A. M.,Gallissot, F.,Langonné, I.,Sabaté, J. P. (2002). Developmental toxicity of N-methyl-2-pyrrolidone administered orally to rats Food and Chemical Toxicology, 40(11), 1705-1712** **HERO ID: 3551103**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance identified by name only.	Medium	2	2	4
	2. Test Substance Source	Source identified by name.	Medium	2	1	2
	3. Test Substance Purity	The reported purity was such that effects likely due to the test substance.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Concurrent negative controls were included.	High	1	2	2
	5. Positive Controls	Positive controls not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Stratified randomization was used so mean body weights were similar among groups on gestation day 0.	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	limited details on preparation were reported. Frequency of preparation and storage were not reported.	Medium	2	1	2
	8. Consistency of Exposure Administration	Exposures were administered consistently.	High	1	1	1
	9. Reporting of Doses/Concentrations	Doses were reported.	High	1	2	2
	10. Exposure Frequency and Duration	Frequency and duration were reported.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of groups and spacing were based on dose-range finding studies.	High	1	1	1
	12. Exposure Route and Method	The route and method were appropriate.	High	1	1	1

N-Methylpyrrolidone

Study reference:	**Saillenfait, A. M.,Gallissot, F.,Langonné, I.,Sabaté, J. P. (2002). Developmental toxicity of N-methyl-2-pyrrolidone administered orally to rats Food and Chemical Toxicology, 40(11), 1705-1712** **HERO ID: 3551103**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Organism	13. Test Animal Characteristics	The source, species, strain, sex, and initial body weight were reported. Health status and age were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	All husbandry conditions were reported except room air changes were reported.	Medium	2	1	2
	15. Number per Group	The number of dams per group was appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Outcome assessment methodology was appropriate.	High	1	2	2
	17. Consistency of Outcome Assessment	Outcomes were assessed consistently.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate.	High	1	1	1
	19. Blinding of Assessors	Blinding not applicable.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses were appropriate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables were reported.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	No health outcomes unrelated to exposure were observed.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical analysis was conducted and appropriate.	High	1	1	1
	24. Reporting of Data	Data were reported for all outcomes.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**38**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.3103**	**Overall Score: Nearest *:**	**1.3**

Study reference:	Saillenfait, A. M.,Gallissot, F.,Langonné, I.,Sabaté, J. P. (2002). Developmental toxicity of N-methyl-2-pyrrolidone administered orally to rats Food and Chemical Toxicology, 40(11), 1705-1712 HERO ID: 3551103					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
		Overall Quality Level:		**High**		

4.9. Animal toxicity evaluation results of Saillenfait et al 2003

Study reference:	**Saillenfait, A. M.,Gallissot, F.,Morel, G. (2003). Developmental toxicity of N-methyl-2-pyrrolidone in rats following inhalation exposure Food and Chemical Toxicology, 41(4), 583-588** **HERO ID: 3551104**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Nomenclature and CASRN were reported	High	1	2	2
	2. Test Substance Source	Source reported	High	1	1	1
	3. Test Substance Purity	Purity (99.5%) such that effects likely due to test substance	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Concurrent negative control animals were included	High	1	2	2
	5. Positive Controls	Positive controls were not required	Not Rated	NA	NA	NA
	6. Randomized Allocation	Females were randomly assigned to exposure groups	High	1	1	1
Exposure Characterization	7. Preparation and Storage of Test Substance	Method of generation and equipment used were reported; however, storage was not.	Medium	2	1	2
	8. Consistency of Exposure Administration	Exposures were administered consistently	High	1	1	1
	9. Reporting of Doses/Concentrations	Target and analytical concentrations were reported. The analytical method was reported and appropriate.	High	1	2	2
	10. Exposure Frequency and Duration	Exposures occurred 6 hr/d on GD 6-20.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The purpose was to set a definitive NOAEL for developmental toxicity, and although not explicitly stated, concentrations appeared to be based on a 2-gen toxicity study in which fetal weights were reduced. The concentrations used were appropriate for the purposes of the study.	Medium	2	1	2

Study reference:	**Saillenfait, A. M.,Gallissot, F.,Morel, G. (2003). Developmental toxicity of N-methyl-2-pyrrolidone in rats following inhalation exposure Food and Chemical Toxicology, 41(4), 583-588** **HERO ID: 3551104**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	12. Exposure Route and Method	Methodological information provided, including an evaluation of aerosol formation (e.g., temperature, humidity). Exposures were conducted in dynamic chamber; however, aerosol particle size was not reported.	Low	3	1	3
Test Organism	13. Test Animal Characteristics	Age, and health status were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Husbandry conditions were reported and appropriate	High	1	1	1
	15. Number per Group	The number of females/group 25-26 was appropriate for the study type and outcomes.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Outcome assessment methodology for maternal and fetal evaluations addressed the outcomes of interest; however, breathing rate/body temperature was not measured.	Low	3	2	6
	17. Consistency of Outcome Assessment	Outcome assessment was carried out consistently among groups	High	1	1	1
	18. Sampling Adequacy	Sampling details were reported and were adequate	High	1	1	1
	19. Blinding of Assessors	No subjective outcomes were assessed.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses were appropriate	High	1	1	1

Study reference:	Saillenfait, A. M.,Gallissot, F.,Morel, G. (2003). Developmental toxicity of N-methyl-2-pyrrolidone in rats following inhalation exposure Food and Chemical Toxicology, 41(4), 583-588 HERO ID: 3551104					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables were reported. However, NMP is an irritant and no measures were made to assess changes in breathing rate or body temperature. The possibility of reflex bradypnea is not eliminated but the results of the study are consistent with oral and dermal study effects on fetal body weight.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	No health differences unrelated to exposure were reported	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were described and appropriate for the dataset	High	1	1	1
	24. Reporting of Data	Data for all outcomes were reported.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**42**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.4483**	**Overall Score: Nearest *:**	**1.4**
		Overall Quality Level:		**High**		

4.10. Animal toxicity evaluation results of Sitarek et al 2008 for a reproductive-male study on reproductive outcomes

Study reference:	**Sitarek, K.,Stetkiewicz, J. (2008). Assessment of reproductive toxicity and gonadotoxic potential of N-methyl-2-pyrrolidone in male rats International Journal of Occupational Medicine and Environmental Health, 21(1), 73-80** **HERO ID: 3540734**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e.,High,Medium, Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	The test substance was identified by name and CASRN.	High	1	2	2
	2. Test Substance Source	Source identified by name.	Medium	2	1	2
	3. Test Substance Purity	Purity not reported. Analytical grade test substance used.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	Concurrent negative control animals were included.	High	1	2	2
	5. Positive Controls	Positive control animals not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Method of randomization for animal allocation was not reported.	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Limited preparation details were provided, and no storage information was provided. It is unclear whether dosing solutions were prepared daily. Since NMP degrades under aerobic conditions, this could have a substantial impact on results.	Low	3	1	3
	8. Consistency of Exposure Administration	It is unclear whether doses were administered consistently, as dosing volumes were not reported.	Low	3	1	3
	9. Reporting of Doses/Concentrations	Doses were reported.	High	1	2	2
	10. Exposure Frequency and Duration	Frequency and duration were reported.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	No justification provided for the number of groups and dose spacing.	Method	2	1	2

Study reference:	**Sitarek, K.,Stetkiewicz, J. (2008). Assessment of reproductive toxicity and gonadotoxic potential of N-methyl-2-pyrrolidone in male rats International Journal of Occupational Medicine and Environmental Health, 21(1), 73-80** **HERO ID: 3540734**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e.,High,Medium, Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	12. Exposure Route and Method	The route and method were appropriate.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The source, species, strain, sex, and age were reported. Initial body weight and health status were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	All husbandry conditions except air changes were reported.	Medium	2	1	2
	15. Number per Group	The number per group was appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Outcome assessment methodology was reported.	High	1	2	2
	17. Consistency of Outcome Assessment	Outcomes were assessed consistently.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate.	High	1	1	1
	19. Blinding of Assessors	Blinding not required.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses were adequate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables were observed.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	No health outcomes unrelated to exposure were reported.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical analysis was described and appropriate.	High	1	1	1
	24. Reporting of Data	Data were presented, but severity and incidence data for histopathological findings were not included.	Low	3	2	6
		Sum of scores:			**29**	**47**

Study reference:	Sitarek, K.,Stetkiewicz, J. (2008). Assessment of reproductive toxicity and gonadotoxic potential of N-methyl-2-pyrrolidone in male rats International Journal of Occupational Medicine and Environmental Health, 21(1), 73-80 HERO ID: 3540734					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e.,High,Medium, Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		1.6207	Overall Score: Nearest *:	1.6
		Overall Quality Level:		High		

4.11. Animal toxicity evaluation results of Sitarek et al 2012 for a single generation reproductive toxicity assessment in rats exposed orally study on hematological and immune, respiratory, endocrine, hepatic, renal, neurological/behavior, thyroid outcomes

Study reference:	**Sitarek, K., Stetkiewicz, J.,W (2012). Evaluation of reproductive disorders in female rats exposed to N-methyl-2-pyrrolidone Birth Defects Research, Part B: Developmental and Reproductive Toxicology, 95(3), 195-201** **HERO ID: 3043651**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance identified by name and CASRN	High	1	2	2
	2. Test Substance Source	Test substance obtained from commercial source but without certification or analytical verification of identity.	Medium	2	1	2
	3. Test Substance Purity	Purity reported to be >98%	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Negative controls were sham-treated with tap water; however, report did not specify whether water was the vehicle for NMP.	Medium	2	2	4
	5. Positive Controls	Positive controls not typical for this study type.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Study did not report how animals were allocated to groups.	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Test material prep and storage were not reported.	Low	3	1	3
	8. Consistency of Exposure Administration	Most exposure details were reported, but time of day of gavage administration was not reported. No inconsistencies in exposure administration were reported.	Medium	2	1	2
	9. Reporting of Doses/Concentrations	Gavage doses were reported in mg/kg bw; initial body weight was not reported.	Medium	2	2	4
	10. Exposure Frequency and Duration	Frequency and duration were reported and suited to the study time.	High	1	1	1

Study reference:	**Sitarek, K., Stetkiewicz, J.,W (2012). Evaluation of reproductive disorders in female rats exposed to N-methyl-2-pyrrolidone Birth Defects Research, Part B: Developmental and Reproductive Toxicology, 95(3), 195-201** **HERO ID: 3043651**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	11. Number of Exposure Groups and Dose Spacing	Three nonzero doses ranging ~7-fold were selected based on fractions of the LD50. Effects were seen at all doses, so it is not clear that the low dose was low enough.	High	1	1	1
	12. Exposure Route and Method	Study does not report whether compound administered neat or in a vehicle. Controls were given tap water, so it is possible that water was the vehicle.	Medium	2	1	2
Test Organism	13. Test Animal Characteristics	The test animal species, strain, sex, life stage, and source (laboratory-maintained colony) were reported. Starting age and body weight were not reported. Test animal was appropriate to the outcome; however, only females were exposed, so effects through the male line could not be assessed.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	All animal husbandry conditions were reported and appropriate.	High	1	1	1
	15. Number per Group	22 to 28 females/group tested.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Endpoints relevant to these outcomes were limited to organ weights, histopathology, and hematocrit.	Low	3	2	6

Study reference:	**Sitarek, K., Stetkiewicz, J.,W (2012). Evaluation of reproductive disorders in female rats exposed to N-methyl-2-pyrrolidone Birth Defects Research, Part B: Developmental and Reproductive Toxicology, 95(3), 195-201** **HERO ID: 3043651**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	17. Consistency of Outcome Assessment	Females of the high dose group that were not pregnant were sacrificed on day 25 post mating, while remaining females were sacrificed after 3 weeks of lactation (the latter had longer exposure durations).	Medium	2	1	2
	18. Sampling Adequacy	All animals were evaluated for all outcomes.	High	1	1	1
	19. Blinding of Assessors	Subjective outcomes not evaluated.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses were reported and adequate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No potentially confounding factors were noted by the authors or apparent in the study.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	There were 2 deaths of nonpregnant females at the high dose, and pneumonia was diagnosed, suggesting possible gavage errors, but the authors did not draw a conclusion with respect to cause of death. This attrition was reported and unlikely to impact the results.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	Statistical analysis was described and conducted; however, it is not clear that all offspring analyses considered the effect of litter size.	Medium	2	1	2
	24. Reporting of Data	Histopathology data were reported qualitatively.	Low	3	2	6
		Sum of scores:			**28**	**50**

Study reference:	Sitarek, K., Stetkiewicz, J.,W (2012). Evaluation of reproductive disorders in female rats exposed to N-methyl-2-pyrrolidone Birth Defects Research, Part B: Developmental and Reproductive Toxicology, 95(3), 195-201 HERO ID: 3043651					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		1.7857	Overall Score: Nearest *:	1.8
		Overall Quality Level:		Medium		

4.12. Animal toxicity evaluation results of Sitarek et al 2012 for single generation reproductive toxicity assessment in rats exposed orally study on reproductive outcomes

Study reference:	**Sitarek, K., Stetkiewicz, J.,W (2012). Evaluation of reproductive disorders in female rats exposed to N-methyl-2-pyrrolidone Birth Defects Research, Part B: Developmental and Reproductive Toxicology, 95(3), 195-201** **HERO ID: 3043651**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance identified by name and CASRN	High	1	2	2
	2. Test Substance Source	Test substance obtained from commercial source but without certification or analytical verification of identity.	Medium	2	1	2
	3. Test Substance Purity	Purity reported to be >98%	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Negative controls were sham-treated with tap water; however, report did not specify whether water was the vehicle for NMP.	Medium	2	2	4
	5. Positive Controls	Positive controls not typical for this study type.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Study did not report how animals were allocated to groups.	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Test material prep and storage were not reported.	Low	3	1	3
	8. Consistency of Exposure Administration	Most exposure details were reported, but time of day of gavage administration was not reported. No inconsistencies in exposure administration were reported.	Medium	2	1	2
	9. Reporting of Doses/Concentrations	Gavage doses were reported in mg/kg bw; initial body weight was not reported.	Medium	2	2	4
	10. Exposure Frequency and Duration	Frequency and duration were reported and suited to the study time.	High	1	1	1

Study reference:	**Sitarek, K., Stetkiewicz, J.,W (2012). Evaluation of reproductive disorders in female rats exposed to N-methyl-2-pyrrolidone Birth Defects Research, Part B: Developmental and Reproductive Toxicology, 95(3), 195-201** **HERO ID: 3043651**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	11. Number of Exposure Groups and Dose Spacing	Three nonzero doses ranging ~7-fold were selected based on fractions of the LD50. Effects were seen at all doses so it is not clear that the low dose was low enough.	High	1	1	1
	12. Exposure Route and Method	Study does not report whether compound administered neat or in a vehicle. Controls were given tap water, so it is possible that water was the vehicle.	Medium	2	1	2
Test Organism	13. Test Animal Characteristics	The test animal species, strain, sex, life stage, and source (laboratory-maintained colony) were reported. Starting age and body weight were not reported. Test animal was appropriate to the outcome; however, only females were exposed, so effects through the male line could not be assessed.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	All animal husbandry conditions were reported and appropriate.	High	1	1	1
	15. Number per Group	22 to 28 females/group tested.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	See footnote at end of page[1]	High	1	2	2

[1] Metrics that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	**Sitarek, K., Stetkiewicz, J.,W (2012). Evaluation of reproductive disorders in female rats exposed to N-methyl-2-pyrrolidone Birth Defects Research, Part B: Developmental and Reproductive Toxicology, 95(3), 195-201** **HERO ID: 3043651**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	17. Consistency of Outcome Assessment	Females of the high dose group that were not pregnant were sacrificed on day 25 post mating, while remaining females were sacrificed after 3 weeks of lactation (the latter had longer exposure durations).	Medium	2	1	2
	18. Sampling Adequacy	All animals were evaluated for all outcomes.	High	1	1	1
	19. Blinding of Assessors	Subjective outcomes not evaluated.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses were reported and adequate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No potentially confounding factors were noted by the authors or apparent in the study.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	There were 2 deaths of nonpregnant females at the high dose, and pneumonia was diagnosed, suggesting possible gavage errors, but the authors did not draw a conclusion with respect to cause of death. This attrition was reported and unlikely to impact the results.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	Statistical analysis was described and conducted; however, it is not clear that all offspring analyses considered the effect of litter size.	Medium	2	1	2
	24. Reporting of Data	See footnote at end of page[1]	High	1	2	2
		Sum of scores:			**28**	**45**

[1] Metrics that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	Sitarek, K., Stetkiewicz, J.,W (2012). Evaluation of reproductive disorders in female rats exposed to N-methyl-2-pyrrolidone Birth Defects Research, Part B: Developmental and Reproductive Toxicology, 95(3), 195-201 HERO ID: 3043651					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		1.6071	Overall Score: Nearest *:	1.6
		Overall Quality Level:		High		

4.13. Animal toxicity evaluation results of Solomon et al 1995 for a 2-generation reproduction/developmental study, inhalation study on reproductive, growth (early life), and development outcomes

Study reference:	**Solomon, H. M., Burgess, B. A., Kennedy, G. L., Jr., Staples, R. E. (1995). 1-methyl-2-pyrrolidone (NMP): Reproductive and developmental toxicity study by inhalation in the rat. Drug and Chemical Toxicology, 18(4), 271-293** **HERO ID: 2761868**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Clearly identified	High	1	2	2
	2. Test Substance Source	Test substance source was reported. No lot or batch number was reported, but this omission of details is not likely to have a substantial impact on results.	Medium	2	1	2
	3. Test Substance Purity	Purity reported (99.9%). Impurities were identified and present in quantities that would not influence the results.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	A concurrent negative control was used and appears to be sham-exposed.	High	1	2	2
	5. Positive Controls	This metric is not rated/applicable for this study type.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Rats were distributed randomly into control and treated groups using a randomized block design based on body weight.	High	1	1	1
Exposure Characterization	7. Preparation and Storage of Test Substance	The test substance preparation, method, and equipment used to generate the vapor were reported and appropriate.	High	1	1	1
	8. Consistency of Exposure Administration	Details of exposure administration were reported and administered consistently across study groups.	High	1	1	1

Study reference:	**Solomon, H. M., Burgess, B. A., Kennedy, G. L., Jr., Staples, R. E. (1995). 1-methyl-2-pyrrolidone (NMP): Reproductive and developmental toxicity study by inhalation in the rat. Drug and Chemical Toxicology, 18(4), 271-293** **HERO ID: 2761868**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	9. Reporting of Doses/Concentrations	Target and analytical concentrations were reported. The analytical high dose was reported as 116.4 ppm (target dose was 130 ppm). It was reported that technical restraints (condensation on the inside of the high dose chambers) prevented attainment of the target dose (130 ppm).	Medium	2	2	4
	10. Exposure Frequency and Duration	The exposure frequency and duration of exposure were appropriately identified.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups and concentrations were not justified by the study authors in the report. This is unlikely to impact results, as the number of exposure groups and spacing of the exposures were adequate to show results relevant to the outcome of interest.	Medium	2	1	2
	12. Exposure Route and Method	A dynamic whole-body chamber was used for vapors that may condense. The high-concentration target of 130 ppm was not attained due to condensation on the inside of the high dose chambers; the actual high-concentration exposure level was measured as 116.4 ppm. The number of air changes/hour was reported to be 12-15.	Medium	2	1	2

Study reference:	**Solomon, H. M., Burgess, B. A., Kennedy, G. L., Jr., Staples, R. E. (1995). 1-methyl-2-pyrrolidone (NMP): Reproductive and developmental toxicity study by inhalation in the rat. Drug and Chemical Toxicology, 18(4), 271-293** **HERO ID: 2761868**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Organism	13. Test Animal Characteristics	The test animal species, strain, sex, age, and starting body weight were reported and obtained from a commercial source. The rats were weighed, and clinical signs were taken on all rats upon arrival and 2 times more before exposure.	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	All husbandry conditions were reported, were adequate, and were the same for control and exposed groups.	High	1	1	1
	15. Number per Group	The number of animals per study group was reported and appropriate for the study type and outcome analysis.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology was reported and addressed the intended outcomes of interest.	High	1	2	2
	17. Consistency of Outcome Assessment	Details of the outcome assessment protocol were reported and outcomes were assessed consistently across study groups.	High	1	1	1
	18. Sampling Adequacy	Sampling was reported and adequate for the outcomes of interest.	High	1	1	1
	19. Blinding of Assessors	The study report reported that investigators assessing outcomes of the developmental were not aware of the exposure group to which any of the dams or offspring belonged to.	High	1	1	1
	20. Negative Control Response	The biological responses of the negative control groups were adequate.	High	1	1	1

Study reference:	**Solomon, H. M., Burgess, B. A., Kennedy, G. L., Jr., Staples, R. E. (1995). 1-methyl-2-pyrrolidone (NMP): Reproductive and developmental toxicity study by inhalation in the rat. Drug and Chemical Toxicology, 18(4), 271-293** **HERO ID: 2761868**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	There were no reported differences among the study groups in initial body weight, but respiratory rates were not reported; this lack of reporting is not likely to have a significant impact on results.	Medium	2	2	4
	22. Health Outcomes Unrelated to Exposure	Details regarding animal attrition and health outcomes unrelated to exposure was reported. It was reported that 2 animals in the control group died during the reproduction phase of the study; one of these deaths was due to a handling injury. There were no differences among groups that would influence the outcome assessment.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were clearly described and appropriate.	High	1	1	1
	24. Reporting of Data	The data for all outcomes were reported by exposure group, sex, and generation and described adequately. Continuous data included means and the respective standard error.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**30**	**37**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.2174**	**Overall Score: Nearest *:**	**1.2**
		Overall Quality Level:		**High**		

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