United States
Environmental Protection Agency

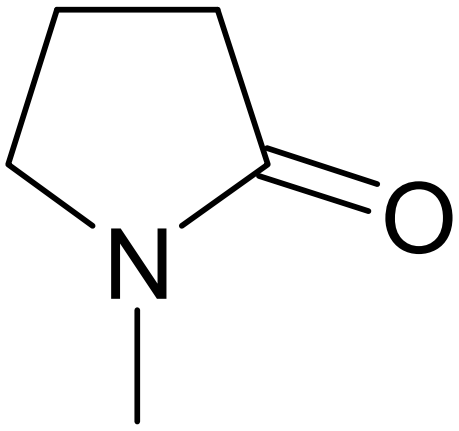
Office of Chemical Safety and
Pollution Prevention

Final Risk Evaluation for n-Methylpyrrolidone

Systematic Review Supplemental File:

Data Quality Evaluation of Human Health Hazard Studies – Animal and *In Vitro* Studies

CASRN: 872-50-4



December 2020

EPA's Office of Pollution Prevention and Toxics (OPPT) developed data quality criteria for animal and *in vitro* studies, presented in the *Application of Systematic Review in TSCA Risk Evaluations* document (EPA Document #740-P1-8001).

This document presents data quality evaluation results for animal and *in vitro* studies evaluated for the NMP Risk Evaluation.

Table Listing

Acute (<24 hr)

Short-term (1-30 days)

Subchronic (30-90 days)

Chronic (>90 days)

Genetic toxicity studies

Developmental and Reproductive

Mechanistic

1 Acute (<24 hr)

Table 1: **Animal toxicity evaluation results of Tatsuno et al., 2014 for an immunotoxicity study on immune outcomes**

Study Citation:	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
Data Type:	Immunotoxicity
HERO ID:	3540753

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	Medium	× 2	4	Test substance identified by name, but more information may be in reference describing preparation of test tapes.
	Metric 2:	Test Substance Source	Low	× 1	3	Source of test substance not identified.
	Metric 3:	Test Substance Purity	Low	× 1	3	Purity not reported
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Animals given a placebo were included.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls not required.
	Metric 6:	Randomized Allocation	Low	× 1	3	Method of randomized allocation was not reported.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Low	× 1	3	Preparation not reported.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Exposures were administered consistently.
	Metric 9:	Reporting of Doses/Concentrations	Medium	× 2	4	Percentages were reported.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Exposure frequencies were reported.
	Metric 11:	Number of Exposure Groups and Dose Spacing	Medium	× 1	2	The number of groups and spacing were reported only.
	Metric 12:	Exposure Route and Method	High	× 1	1	The route and method appear appropriate for the test substance and the purposes of the study.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	The source, species, strain, and age were reported. Health status and initial body weight were not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	× 1	3	Husbandry conditions were not reported.
	Metric 15:	Number per Group	High	× 1	1	The number of animals per group were appropriate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	Outcome assessment methodology was described.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate.

Continued on next page . . .

. . . continued from previous page

Study Citation:	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
Data Type:	Immunotoxicity
HERO ID:	3540753

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding not required.
	Metric 20:	Negative Control Response	High	× 1	1	Negative and placebo responses were reported and appropriate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	No confounding variables were observed.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health outcomes unrelated to exposure were reported.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were appropriate.
	Metric 24:	Reporting of Data	High	× 2	2	Outcome data were reported.
Overall Quality Determination‡			~~High~~ ⟶ Medium§		~~1.6~~	
Extracted			No			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

§ Evaluator's explanation for rating change: "Additional information should be obtained from the reference."

Table 2: **Animal toxicity evaluation results of Lashmar et al., 1989 for an irritation study, dermal 24-hour study on irritation outcomes**

Study Citation:	Lashmar, UT; 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
Data Type:	irritation study, dermal 24-hour
HERO ID:	3539872

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	Medium	× 2	4	Test substance identified by name; CASRN not reported.
	Metric 2:	Test Substance Source	Medium	× 1	2	The source manufacturer was reported, but batch/lot numbers were not; this omission is unlikely to have a substantial impact on results.
	Metric 3:	Test Substance Purity	Low	× 1	3	Test substance reported to be "reagent grade," but no specific purity was reported.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	Medium	× 2	4	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.
	Metric 5:	Positive Controls	Not Rated	NA	NA	The use of a positive control is not indicated by this study type.
	Metric 6:	Randomized Allocation	Low	× 1	3	The study did not report how animals were allocated to study groups.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Low	× 1	3	Test substance preparation was briefly reported. There is a lack of reporting of the test substance storage.
	Metric 8:	Consistency of Exposure Administration	Medium	× 1	2	Details of exposure protocol were limited; however, this deficiency is unlikely to have a substantial impact on the results.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Administered doses are reported.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Exposure duration (24- hours) was reported and appropriate for the study.
	Metric 11:	Number of Exposure Groups and Dose Spacing	Medium	× 1	2	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.
	Metric 12:	Exposure Route and Method	Medium	× 1	2	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.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Lashmar, UT; 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
Data Type:	irritation study, dermal 24-hour
HERO ID:	3539872

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	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.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	× 1	3	Animal husbandry conditions were not sufficiently reported to determine whether husbandry was adequate.
	Metric 15:	Number per Group	High	× 1	1	The number of animals per study group was reported (3) and appropriate for the study type.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	Medium	× 2	4	The outcome assessment methodology was partially addressed for the intended outcomes of interest reported
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	The assessment protocol were reported and consistent across study groups and chemicals tested.
	Metric 18:	Sampling Adequacy	High	× 1	1	Details regarding sampling for the outcomes of interest were reported and adequate.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	This metric is not applicable for initial histopathology review; therefore, is not rated for this study.
	Metric 20:	Negative Control Response	High	× 1	1	The untreated control and 1% gel control response was adequate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	× 2	4	PVC and PVCD were used for occluded dermal exposure, it is unclear how this may have impacted the results.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	× 1	2	There is no reporting for attrition and/or health outcomes unrelated to exposure, though it is unlikely to have a substantial impact on results.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	Medium	× 1	2	No statistical analysis methods or statistical results were reported; however, calculation methods for irritation scores were described.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Lashmar, UT; 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
Data Type:	irritation study, dermal 24-hour
HERO ID:	3539872

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 24: Reporting of Data	Medium	× 2	4	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.
Overall Quality Determination‡		Medium		1.9	
Extracted		No			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

2 Short-term (1-30 days)

Table 3: **Animal toxicity evaluation results of Boenisch et al., 2012 for a 19-day immunotoxicity (inhalation) study on hematological, immune, and respiratory outcomes**

Study Citation:	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					
Data Type:	19-day immunotoxicity (inhalation)					
HERO ID:	2333837					
Domain		Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	The test substance was identified definitively.
	Metric 2:	Test Substance Source	Low	× 1	3	The source and batch/lot number of the test substance was not reported.
	Metric 3:	Test Substance Purity	Low	× 1	3	Purity and grade of the test substance were not reported.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	The study authors reported using a concurrent negative control group.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls were not required.
	Metric 6:	Randomized Allocation	Low	× 1	3	The study authors did not report how animals were allocated to study groups.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Low	× 1	3	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.
	Metric 8:	Consistency of Exposure Administration	Low	× 1	3	Critical exposure details, including the methods for generating atmosphere in inhalation chambers, were not reported.
	Metric 9:	Reporting of Doses/Concentrations	Medium	× 2	4	Mean concentrations were measured (as reported in supplemental file S1).
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	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).
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	The number of exposure groups and spacing were reported and were relevant for the assessment.
	Metric 12:	Exposure Route and Method	Low	× 1	3	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).

Continued on next page . . .

. . . continued from previous page

Study Citation: 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
Data Type: 19-day immunotoxicity (inhalation)
HERO ID: 2333837

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	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.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	× 1	1	All husbandry conditions were reported and were adequate and the same for the control and exposed populations.
	Metric 15:	Number per Group	Low	× 1	3	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).
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	The outcome assessment methodology addressed or reported the intended outcomes of interest and was sensitive for the outcomes of interest.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Details of the outcome assessment protocol were reported, and outcomes were assessed consistently across study groups.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling of the outcomes of interest were adequate.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding is not required for objective outcomes.
	Metric 20:	Negative Control Response	High	× 1	1	The negative control responses were reported and acceptable.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	× 2	6	Respiratory rate measurement was not reported. This is may impact results since NMP is a potential respiratory irritant.
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	× 1	3	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.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were reported and were appropriate for the data sets.

Continued on next page . . .

. . . continued from previous page

Study Citation:	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
Data Type:	19-day immunotoxicity (inhalation)
HERO ID:	2333837

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 24: Reporting of Data	High	× 2	2	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.
Overall Quality Determination‡		Medium		1.8	
Extracted		No			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

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

Study Citation:	Lee, KP; Chromey, NC; Culik, R; Barnes, JR; Schneider, PW (1987). Toxicity of N-methyl-2-pyrrolidone (NMP): Teratogenic, subchronic, and two-year inhalation studies Fundamental and Applied Toxicology, 9(2), 222-235					
Data Type:	4-wk inhalation					
HERO ID:	3539878					
Domain		Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Structure, nomenclature, physiochemical properties provided
	Metric 2:	Test Substance Source	Low	× 1	3	Source not identified
	Metric 3:	Test Substance Purity	Medium	× 1	2	Purity such that effects due to test substance.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Negative controls were included
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls not required
	Metric 6:	Randomized Allocation	Low	× 1	3	Method of allocation was not described
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Medium	× 1	2	Preparation of test atmospheres was described, storage of the test material was not.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Exposures were administered consistently
	Metric 9:	Reporting of Doses/Concentrations	Low	× 2	6	Aerosol particle size and MMAD were not reported.
	Metric 10:	Exposure Frequency and Duration	Medium	× 1	2	Duration of exposure did not extend throughout organogenesis.
	Metric 11:	Number of Exposure Groups and Dose Spacing	Medium	× 1	2	Rationale for dose selection was not provided
	Metric 12:	Exposure Route and Method	Low	× 1	3	Route was appropriate, but insufficient detail was provided on the method (e.g., humidity, number of air changes per hour)
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Low	× 2	6	The source, species, strain, and sex were provided; age, and initial body weight, and health status were not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	× 1	3	Husbandry was not adequately reported.
	Metric 15:	Number per Group	High	× 1	1	The number of animals exposed in each group was adequate
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	Low	× 2	6	Breathing rate and body temperature were not measured.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Lee, KP; Chromey, NC; Culik, R; Barnes, JR; Schneider, PW (1987). Toxicity of N-methyl-2-pyrrolidone (NMP): Teratogenic, subchronic, and two-year inhalation studies Fundamental and Applied Toxicology, 9(2), 222-235
Data Type:	4-wk inhalation
HERO ID:	3539878

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate for the outcomes
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Subjective outcomes were not assessed
	Metric 20:	Negative Control Response	High	× 1	1	Negative controls responded appropriately
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	× 2	6	Test animals showed signs of lethargy and irregular respiration.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	None were reported
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	Medium	× 1	2	Statistical methods were appropriate when applied, but all outcomes were not analyzed.
	Metric 24:	Reporting of Data	High	× 2	2	Data were reported for outcomes
Overall Quality Determination‡			Medium		2.0	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 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 Citation:	Malek, DE; Malley, LA; Slone, TW; Elliott, GS; Kennedy, GL; Mellert, W; Deckardt, K; Gembardt, C; Hildebrand, B; Murphy, SR; Bower, DB; Wright, GA (1997). Repeated dose toxicity study (28 days) in rats and mice with N-methylpyrrolidone (NMP) Drug and Chemical Toxicology, 20(1-2), 63-77
Data Type:	25-day oral, rats and mice
HERO ID:	3539910

Domain		Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance identified by name and CASRN.
	Metric 2:	Test Substance Source	High	× 1	1	The source was identified.
	Metric 3:	Test Substance Purity	High	× 1	1	The reported purity was such that effects likely due to the test substance.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Concurrent negative control animals were included.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls not required.
	Metric 6:	Randomized Allocation	Medium	× 1	2	Animals were allocated by computerized stratified randomization so no statistically significant differences among body weights were observed.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Low	× 1	3	Limited preparation details were presented; however, no information on NMP analytical concentration, storage or stability were reported.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Exposures were administered consistently.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Frequency and duration of exposure were reported.
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	The number of exposure groups and spacing were reported and justified.
	Metric 12:	Exposure Route and Method	High	× 1	1	The exposure route and method were appropriate.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	The source, species, strain, sex, age, and initial body weight, and health status were reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	× 1	2	All husbandry conditions except room air changes were reported.
	Metric 15:	Number per Group	High	× 1	1	The numbers of animals per group were appropriate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	Outcome assessment methodology was appropriate.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Malek, DE; Malley, LA; Slone, TW; Elliott, GS; Kennedy, GL; Mellert, W; Deckardt, K; Gembardt, C; Hildebrand, B; Murphy, SR; Bower, DB; Wright, GA (1997). Repeated dose toxicity study (28 days) in rats and mice with N-methylpyrrolidone (NMP) Drug and Chemical Toxicology, 20(1-2), 63-77
Data Type:	25-day oral, rats and mice
HERO ID:	3539910

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding was not required.
	Metric 20:	Negative Control Response	High	× 1	1	Negative control responses were appropriate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	No confounding variables were reported.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health effects unrelated to exposure were reported.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were reported and appropriate.
	Metric 24:	Reporting of Data	High	× 2	2	Data were reported.
Overall Quality Determination‡			~~High~~ ⟶ High§		~~1.1~~	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

§ Evaluator's explanation for rating change: "Although no information on NMP analytical concentration, storage or stability were reported; the study protocol is valid."

Table 6: **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 Citation:	Haskell Laboratories (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					
Data Type:	4-wk inhalation, mortality, histopathology					
HERO ID:	3563360					
Domain		Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance identified by name and CASRN.
	Metric 2:	Test Substance Source	Low	× 1	3	Test substance submitted by identified persons.
	Metric 3:	Test Substance Purity	Low	× 1	3	Purity was not reported.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Concurrent controls were used.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls were not required.
	Metric 6:	Randomized Allocation	Low	× 1	3	Randomized allocation of animals was not reported.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Medium	× 1	2	Methods and equipment used to generate the aerosol were reported; however, storage of the test material was not reported.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Exposures were administered consistently.
	Metric 9:	Reporting of Doses/Concentrations	Unacceptable	× 2	8	Nominal and measured concentrations were reported, but particle size and MMAD were not reported.
	Metric 10:	Exposure Frequency and Duration	Medium	× 1	2	Duration was reported, but frequency, in terms of days/week, was reported only as 21 six- hour exposures
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	The number of groups and spacing were reported and justified.
	Metric 12:	Exposure Route and Method	Low	× 1	3	The number of air changes in the exposure chamber was not reported.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	The species, strain, sex, and initial body weight were reported. The age, health status, and source were not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	× 1	3	Husbandry conditions were not reported.
	Metric 15:	Number per Group	High	× 1	1	The number of animals per group was appropriate.
Domain 5: Outcome Assessment						

Continued on next page . . .

. . . continued from previous page

Study Citation:	Haskell Laboratories (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
Data Type:	4-wk inhalation, mortality, histopathology
HERO ID:	3563360

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 16:	Outcome Assessment Methodology	Low	× 2	6	Breathing rates and body temperature were not measured to rule out reflex bradypnea from irritancy.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding was not required.
	Metric 20:	Negative Control Response	High	× 1	1	Negative controls responded appropriately.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	× 2	6	Test animals showed signs of lethargy and irregular respiration which persisted until the end of each exposure.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health outcomes unrelated to exposures were reported.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	Medium	× 1	2	Statistical methods were described in the appendices and were appropriate. Analysis of histopathological results was not conducted.
	Metric 24:	Reporting of Data	High	× 2	2	Data were reported.
Overall Quality Determination‡			Unacceptable⋆⋆		2.0	
Extracted			No			

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 7: **Animal toxicity evaluation results of Gopinathan et al., 2013 for a 5-day oral study on clinical chemistry/biochemical, renal, and hematological and immune outcomes**

Study Citation:	Gopinathan, S; O'Neill, E; Rodriguez, LA; Champ, R; Phillips, M; Nouraldeen, Amr; Wendt, M; Wilson, AGE; Kramer, JA (2013). In vivo toxicology of excipients commonly employed in drug discovery in rats Journal of Pharmacological and Toxicological Methods, 68(2), 284-295
Data Type:	5-day oral
HERO ID:	3037621

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	Medium	× 2	4	The test substance was identified.
	Metric 2:	Test Substance Source	Medium	× 1	2	The source of the test substance was reported, but a batch/lot number was not reported.
	Metric 3:	Test Substance Purity	Low	× 1	3	Test substance purity was not reported, but all substances tested in the study were stated to have been of reagent or pharmacopeia grade.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	Low	× 2	6	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).
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls were not required.
	Metric 6:	Randomized Allocation	Medium	× 1	2	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.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Low	× 1	3	Preparation and storage of the test substance were not reported.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	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).
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Administered doses were reported without ambiguity.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	The exposure frequency and duration were reported and were appropriate for the study type and outcomes of interest (acute toxicity).
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	The number of exposure groups and dose spacing was reported and was acceptable.

Continued on next page . . .

. . . continued from previous page

Study Citation: Gopinathan, S; O'Neill, E; Rodriguez, LA; Champ, R; Phillips, M; Nouraldeen, Amr; Wendt, M; Wilson, AGE; Kramer, JA (2013). In vivo toxicology of excipients commonly employed in drug discovery in rats Journal of Pharmacological and Toxicological Methods, 68(2), 284-295
Data Type: 5-day oral
HERO ID: 3037621

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Exposure Route and Method	High	× 1	1	The exposure route and method were reported and were acceptable.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	The test animal source, species, strain, and sex were reported; however, age, health status, and starting body weights were not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	× 1	3	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.
	Metric 15:	Number per Group	High	× 1	1	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.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	The outcome assessment methodology addressed or reported the intended outcomes of interest and was sensitive for the outcomes of interest (acute effects).
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Details of the outcome assessment methodology were reported, and outcomes were assessed consistently across study groups using the same protocol for all groups.
	Metric 18:	Sampling Adequacy	High	× 1	1	Details regarding sampling for the outcomes of interest were reported and the study used adequate sampling for the outcomes of interest.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding was not required.
	Metric 20:	Negative Control Response	High	× 1	1	The negative control responses were reported and acceptable.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	There were no reported differences among the study groups that would influence the outcome.
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	× 1	3	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.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were clearly described and were appropriate for the data sets.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Gopinathan, S; O'Neill, E; Rodriguez, LA; Champ, R; Phillips, M; Nouraldeen, Amr; Wendt, M; Wilson, AGE; Kramer, JA (2013). In vivo toxicology of excipients commonly employed in drug discovery in rats Journal of Pharmacological and Toxicological Methods, 68(2), 284-295
Data Type:	5-day oral
HERO ID:	3037621

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 24: Reporting of Data	Low	× 2	6	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.
Overall Quality Determination‡		~~Medium~~ ⟶ Medium§		~~1.8~~	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

§ Evaluator's explanation for rating change: "I would downgrade this paper to medium based on a relatively large number of reporting deficiencies (e.g., preparation and storage of the test substance; incomplete reporting of necropsy results)."

Table 8: **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 Citation:	N-Methylpyrrolidone Producers Group (1994). Repeated dose toxicity with N-Methylpyrrolidone in B6C3F1 mice Administration in the diet for 4 weeks (Range-finding study)
Data Type:	4-wk dietary study
HERO ID:	4214115

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	The test substance was identified definitely and CASRN reported.
	Metric 2:	Test Substance Source	High	× 1	1	The source of the testing laboratory (industry sponsored) test substance was reported, including manufacturer and batch/lot number.
	Metric 3:	Test Substance Purity	High	× 1	1	The test substance purity was reported.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Study authors reported using an appropriate concurrent negative control group.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Not required for study type
	Metric 6:	Randomized Allocation	Medium	× 1	2	Randomization list was drawn up by a computer based on body weight (laboratory data processing, Dept of Toxicology, BASF)
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	High	× 1	1	The test substance preparation and storage conditions were reported and appropriate for the test substance.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Details of exposure administration were reported, and exposures were administered consistently across study groups.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	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.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	The exposure frequency and duration of exposure were reported.
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	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.
	Metric 12:	Exposure Route and Method	High	× 1	1	The route and method of exposure were reported and were suited to the test substance.

Continued on next page . . .

. . . continued from previous page

Study Citation: N-Methylpyrrolidone Producers Group (1994). Repeated dose toxicity with N-Methylpyrrolidone in B6C3F1 mice Administration in the diet for 4 weeks (Range-finding study)
Data Type: 4-wk dietary study
HERO ID: 4214115

Domain	Metric		Rating†	MWF*	Score	Comments††
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	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.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	× 1	1	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.
	Metric 15:	Number per Group	Medium	× 1	2	The reported number of animals per study group was lower than the typical number used in studies of the same or similar type.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	The outcome assessment methodology addressed or reported the intended outcome(s) of interest and was sensitive for the outcomes(s) of interest.
	Metric 17:	Consistency of Outcome Assessment	Medium	× 1	2	Incomplete reporting of minor details of outcome assessment protocol execution, but these uncertainties or limitations are unlikely to have a substantial impact on results.
	Metric 18:	Sampling Adequacy	High	× 1	1	Details regarding sampling for the outcome(s) of interest were reported and the study used adequate sampling for the outcome(s) of interest.
	Metric 19:	Blinding of Assessors	Low	× 1	3	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.
	Metric 20:	Negative Control Response	High	× 1	1	The biological responses of the negative control group(s) were adequate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	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.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	Details regarding animal attrition and health outcomes unrelated to exposure were reported for each study group.
Domain 7: Data Presentation and Analysis						

Continued on next page . . .

. . . continued from previous page

Study Citation:	N-Methylpyrrolidone Producers Group (1994). Repeated dose toxicity with N-Methylpyrrolidone in B6C3F1 mice Administration in the diet for 4 weeks (Range-finding study)
Data Type:	4-wk dietary study
HERO ID:	4214115

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were clearly described and appropriate for dataset(s).
	Metric 24:	Reporting of Data	High	× 2	2	Data for exposure-related findings were presented for all outcomes by exposure group.
Overall Quality Determination‡			High		1.2	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 9: **Animal toxicity evaluation results of N-Methylpyrrolidone Producers Group 1994 for 28-day diet study in rats on systemic and reproductive effects**

Study Citation:	N-Methylpyrrolidone Producers Group (1994). Subchronic Oral Toxicity: 28-day Feeding study in Rats with N-Methylpyrrolidone (NMP)					
Data Type:	28-day diet rat-systemic and repro effects					
HERO ID:	4214124					
Domain		Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance identified by name, synonyms, CASRN, form, and structure.
	Metric 2:	Test Substance Source	High	× 1	1	The source was identified along with production date, and tank number.
	Metric 3:	Test Substance Purity	High	× 1	1	Purity and composition are such that effects are likely due to the test substance.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Concurrent negative control animals were included.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive control animals not required.
	Metric 6:	Randomized Allocation	Medium	× 1	2	Allocation wad by computerized stratified randomization to prevent no statistically significant differences among mean body weights by sex.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	High	× 1	1	Preparation and storage conditions were appropriate. Stability, homogeneity, and concentration analysis were conducted and appropriate.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Diets were administered consistently.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported without ambiguity.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Exposure frequency and duration were reported.
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	The number of exposure groups and dose spacing were based on the results of previous studies.
	Metric 12:	Exposure Route and Method	High	× 1	1	The route and method were as specified in TPA TSCA testing consent order.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	The source, species, strain, sex, age, initial body weight, and health status were reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	× 1	1	All husbandry conditions were reported and were appropriate.
	Metric 15:	Number per Group	High	× 1	1	The number of animals per group was appropriate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	Outcome assessment methodology was reported.

Continued on next page . . .

. . . continued from previous page

Study Citation:	N-Methylpyrrolidone Producers Group (1994). Subchronic Oral Toxicity: 28-day Feeding study in Rats with N-Methylpyrrolidone (NMP)
Data Type:	28-day diet rat-systemic and repro effects
HERO ID:	4214124

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcome assessment was consistent across groups.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate for the outcomes of interest.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding not required for the outcomes.
	Metric 20:	Negative Control Response	High	× 1	1	Negative controls responded appropriately.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	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.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health outcomes unrelated to exposure were reported.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical analyses were described and appropriate.
	Metric 24:	Reporting of Data	High	× 2	2	All outcomes were reported.
Overall Quality Determination‡			High		1.0	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

3 Subchronic (30-90 days)

Table 10: **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 Citation:	Malley, LA; Kennedy, GL; Elliott, GS; Slone, TW; Mellert, W; Deckardt, K; Gembardt, C; Hildebrand, B; Parod, RJ; Mccarthy, TJ; Griffiths, JC (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
Data Type:	90-day oral rats and mice
HERO ID:	3539912

Domain		Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance identified by name and CASRN.
	Metric 2:	Test Substance Source	Medium	× 1	2	The source was identified.
	Metric 3:	Test Substance Purity	High	× 1	1	The reported purity was such that effects likely due to test substance.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Negative control animals were included.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls not required.
	Metric 6:	Randomized Allocation	Medium	× 1	2	Animals allocated by computerized stratified randomization.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	High	× 1	1	Limited preparation details were reported, but no storage information was presented. Stability of the test substance in the diet was established.
	Metric 8:	Consistency of Exposure Administration	Medium	× 1	2	Exposures were administered consistently.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Frequency and duration were reported.
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	The number of exposure groups and spacing were reported and justified.
	Metric 12:	Exposure Route and Method	High	× 1	1	The route and method were reported.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	The source, species, strain, sex, age, initial body weight, and health status were reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	× 1	2	All conditions except for room air changes were reported.
	Metric 15:	Number per Group	High	× 1	1	the number of animals per group was appropriate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	Outcome assessment methodology was reported.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Malley, LA; Kennedy, GL; Elliott, GS; Slone, TW; Mellert, W; Deckardt, K; Gembardt, C; Hildebrand, B; Parod, RJ; Mccarthy, TJ; Griffiths, JC (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
Data Type:	90-day oral rats and mice
HERO ID:	3539912

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate.
	Metric 19:	Blinding of Assessors	Medium	× 1	2	Experimenters conducting the FOB evaluations were blind with respect to the exposure group of each animal.
	Metric 20:	Negative Control Response	High	× 1	1	Negative control responses were appropriate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	No confounding variables were reported.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health outcomes unrelated to exposure were observed.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were appropriate.
	Metric 24:	Reporting of Data	High	× 2	2	Data were reported.
Overall Quality Determination‡			High		1.2	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 11: **Animal toxicity evaluation results of BASF 1995 for a 90-day diet mouse-liver toxicity study on hepatic outcomes**

Study Citation:	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					
Data Type:	90-day diet mouse-liver toxicity					
HERO ID:	3585204					
Domain		Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance identified by name and CASRN
	Metric 2:	Test Substance Source	Medium	× 1	2	Source not identified but production container was listed.
	Metric 3:	Test Substance Purity	High	× 1	1	Purity (99.8%) determined by gas chromatography and such that effects likely due to the test substance.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Concurrent negative controls were used.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls not required.
	Metric 6:	Randomized Allocation	Medium	× 1	2	Animals allocated by weight using a computerized randomization list.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	High	× 1	1	Preparation and storage details were provided. Stability, homogeneity, and concentration tests were conducted.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Exposures were administered consistently.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Frequency and duration of exposures were reported.
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	The number of groups and dose spacing were reported and justified.
	Metric 12:	Exposure Route and Method	High	× 1	1	Route and method were appropriate.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	The source, species, strain, sex, initial body weight, and health status were reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	× 1	2	All husbandry conditions except air changes were reported.
	Metric 15:	Number per Group	High	× 1	1	The number of animals per group was appropriate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	Outcome assessment methodology was appropriate.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding not required.

Continued on next page . . .

. . . continued from previous page

Study Citation:	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
Data Type:	90-day diet mouse-liver toxicity
HERO ID:	3585204

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 20: Negative Control Response	High	× 1	1	Negative control responses were appropriate.
Domain 6: Confounding / Variable Control					
	Metric 21: Confounding Variables in Test Design and Procedures	High	× 2	2	No confounding variables were observed.
	Metric 22: Health Outcomes Unrelated to Exposure	High	× 1	1	No health outcomes unrelated to exposure were observed.
Domain 7: Data Presentation and Analysis					
	Metric 23: Statistical Methods	High	× 1	1	Statistical analysis was conducted and appropriate.
	Metric 24: Reporting of Data	High	× 2	2	Data were presented.
Overall Quality Determination‡		High		1.1	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 12: **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 Citation:	Becci, PJ; Gephart, LA; Koschier, FJ; Johnson, WD; Burnette, LW (1983). Subchronic feeding study in beagle dogs of N-methylpyrrolidone Journal of Applied Toxicology, 3(2), 83-86					
Data Type:	13-wk diet dogs					
HERO ID:	3539728					
Domain		Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance identified by name and CASRN.
	Metric 2:	Test Substance Source	Low	× 1	3	The test substance was obtained from the study sponsor (GAF Corp).
	Metric 3:	Test Substance Purity	High	× 1	1	The purity of the test substance was reported (99.9%).
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Negative control animals were included.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls were not required.
	Metric 6:	Randomized Allocation	Low	× 1	3	Allocation method was not reported.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Low	× 1	3	Preparation was reported, but storage and analysis was not.
	Metric 8:	Consistency of Exposure Administration	Medium	× 1	2	Exposures were adjusted weekly according to body-weight in treated but not control animals.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported.
	Metric 10:	Exposure Frequency and Duration	Low	× 1	3	The pattern of exposure is inadequate for assessing the outcome of interest(developmental toxicity).
	Metric 11:	Number of Exposure Groups and Dose Spacing	Low	× 1	3	The number of groups and spacing were reported, but not justified.
	Metric 12:	Exposure Route and Method	Low	× 1	3	It is unclear whether the test diet was prepared daily.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	The source, species, strain, and age were reported. Health status and initial body weight were not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	× 1	2	Humidity, housing, and room air changes were not reported.
	Metric 15:	Number per Group	High	× 1	1	The number of animals was appropriate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	Outcome assessment methodology was reported and appropriate.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Becci, PJ; Gephart, LA; Koschier, FJ; Johnson, WD; Burnette, LW (1983). Subchronic feeding study in beagle dogs of N-methylpyrrolidone Journal of Applied Toxicology, 3(2), 83-86
Data Type:	13-wk diet dogs
HERO ID:	3539728

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding was not required.
	Metric 20:	Negative Control Response	High	× 1	1	Negative control responses were appropriate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	× 2	6	It is unclear why the test substance was diluted in corn oil or how this may impact toxicity.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health outcomes unrelated to exposure were observed.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	Medium	× 1	2	Statistical methods were described with some omissions that may impact results.
	Metric 24:	Reporting of Data	High	× 2	2	Data were reported.
Overall Quality Determination‡			Medium		1.7	
Extracted			No			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

4 Chronic (>90 days)

Table 13: **Animal toxicity evaluation results of Malley et al., 2001 for an oral cancer rats and mice study on cancer, hepatic, and renal outcomes**

Study Citation:	Malley, LA; Kennedy, GL; Elliott, GS; Slone, TW; Mellert, W; Deckardt, K; Kuttler, K; Hildebrand, B; Banton, MI; Parod, RJ; Griffiths, JC (2001). Chronic toxicity and oncogenicity of N-methylpyrrolidone (NMP) in rats and mice by dietary administration Drug and Chemical Toxicology, 24(4), 315-338
Data Type:	Oral cancer rats and mice
HERO ID:	3539913

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance identified by name and CASRN.
	Metric 2:	Test Substance Source	Medium	× 1	2	Source identified by name.
	Metric 3:	Test Substance Purity	High	× 1	1	The reported purity was such that effects are likely due to the test substance.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Negative control animals were included.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls were not required.
	Metric 6:	Randomized Allocation	Medium	× 1	2	allocation was by computerized stratified randomization.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Medium	× 1	2	Preparation details were limited, but stability, homogeneity, and concentration analysis were conducted.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Exposures were administered consistently.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported.
	Metric 10:	Exposure Frequency and Duration	Medium	× 1	2	Frequency and duration information were reported.
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	The number of groups and spacing were reported and justified.
	Metric 12:	Exposure Route and Method	High	× 1	1	Route and method were appropriate.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	The source, species, strain, age, initial body weight, and health status were reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	× 1	2	All conditions were reported except for room air changes.
	Metric 15:	Number per Group	High	× 1	1	The number of animals was appropriate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	Outcome assessment methodology was appropriate.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Malley, LA; Kennedy, GL; Elliott, GS; Slone, TW; Mellert, W; Deckardt, K; Kuttler, K; Hildebrand, B; Banton, MI; Parod, RJ; Griffiths, JC (2001). Chronic toxicity and oncogenicity of N-methylpyrrolidone (NMP) in rats and mice by dietary administration Drug and Chemical Toxicology, 24(4), 315-338
Data Type:	Oral cancer rats and mice
HERO ID:	3539913

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were administered consistently.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding was not required.
	Metric 20:	Negative Control Response	High	× 1	1	Negative control responses were appropriate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	No confounding variables were reported.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health outcomes unrelated to exposures were reported.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were reported and appropriate.
	Metric 24:	Reporting of Data	High	× 2	2	Data were reported.
Overall Quality Determination‡			High		1.2	
Extracted			No			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 14: **Animal toxicity evaluation results of N-Methylpyrrolidone Producers Group 1999 for 18-month oral cancer study in mice on cancer and hepatic outcomes**

Study Citation:	N-Methylpyrrolidone Producers Group (1999). N-methylpyrrolidone - carcinogenicity study in B6C3F1 mice, administration in the diet for 18 months, with cover letter dated 11/23/1999
Data Type:	18-month oral cancer mice
HERO ID:	3566221

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance identified by name and CASRN.
	Metric 2:	Test Substance Source	Medium	× 1	2	The source was not identified but the date of manufacture and container number were reported.
	Metric 3:	Test Substance Purity	High	× 1	1	The purity was determined by gas chromatography and such that effects likely due to test substance.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Negative controls were included.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls were not required.
	Metric 6:	Randomized Allocation	Medium	× 1	2	Animals were distributed by weight using a computerized randomization list.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	High	× 1	1	Preparation methods, storage conditions, and results from stability testing were reported and appropriate.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Exposures were administered consistently.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Duration and frequency were reported.
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	The number of groups and spacing were reported and justified.
	Metric 12:	Exposure Route and Method	High	× 1	1	The exposure route and method were appropriate.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	The source, species, strain, sex, , age, initial body weight, and health status were reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	× 1	2	All husbandry conditions except air changes were reported..
	Metric 15:	Number per Group	High	× 1	1	The number of animals per group was appropriate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	Outcome assessment methodology was appropriate.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate.

Continued on next page . . .

. . . continued from previous page

Study Citation:	N-Methylpyrrolidone Producers Group (1999). N-methylpyrrolidone - carcinogenicity study in B6C3F1 mice, administration in the diet for 18 months, with cover letter dated 11/23/1999
Data Type:	18-month oral cancer mice
HERO ID:	3566221

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 19: Blinding of Assessors	Not Rated	NA	NA	Blinding not required.
	Metric 20: Negative Control Response	High	× 1	1	Negative control responses were appropriate.
Domain 6: Confounding / Variable Control					
	Metric 21: Confounding Variables in Test Design and Procedures	High	× 2	2	No confounding variables were reported.
	Metric 22: Health Outcomes Unrelated to Exposure	High	× 1	1	No health outcomes unrelated to exposure were observed.
Domain 7: Data Presentation and Analysis					
	Metric 23: Statistical Methods	High	× 1	1	Statistical methods were described in detail and suited to the data.
	Metric 24: Reporting of Data	High	× 2	2	Data for all outcomes were reported.
Overall Quality Determination‡		High		1.1	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 15: **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 Citation:	DuPont (E. I. Dupont De Nemours and Company) (1982). 2-year inhalation study with n-methyl-2-pyrrolidone in rats (final) with cover letter dated 083090
Data Type:	2-year inhalation in rats
HERO ID:	4214102

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	Medium	× 2	4	Test substance identified by name.
	Metric 2:	Test Substance Source	Low	× 1	3	Sponsor identified as source of test substance.
	Metric 3:	Test Substance Purity	Medium	× 1	2	Purity such that effects likely due to the test substance. Impurities were identified.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Negative controls were used.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls were not required.
	Metric 6:	Randomized Allocation	Medium	× 1	2	Selective allocation was used so that the mean body weights were equal across groups and sex.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Medium	× 1	2	Generation of vapors were reported and appropriate; storage of test substance was not reported.
	Metric 8:	Consistency of Exposure Administration	Low	× 1	3	Exposure periods were occasionally shorter than 6 hours or missed entirely because of mechanical problems.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Concentrations were presented without ambiguity.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Frequency and duration were reported and appropriate.
	Metric 11:	Number of Exposure Groups and Dose Spacing	Medium	× 1	2	The number of exposure groups and dose spacing were appropriate but not justified.
	Metric 12:	Exposure Route and Method	High	× 1	1	Deficiencies in reporting of aerosol formation.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	The source, species, strain, age, health status, sex, and body weight at start of test were reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	× 1	1	All husbandry conditions were reported.
	Metric 15:	Number per Group	High	× 1	1	The number of animals per group was appropriate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	Low	× 2	6	Breathing rate was not reported.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcome assessments were consistent.

Continued on next page . . .

. . . continued from previous page

Study Citation: DuPont (E. I. Dupont De Nemours and Company) (1982). 2-year inhalation study with n-methyl-2-pyrrolidone in rats (final) with cover letter dated 083090
Data Type: 2-year inhalation in rats
HERO ID: 4214102

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate for the endpoints examined.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding was not required.
	Metric 20:	Negative Control Response	High	× 1	1	Negative control responses were appropriate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	× 2	6	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.
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	× 1	3	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.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	Low	× 1	3	Statistical methods were described. It does not appear that incidence data were analyzed.
	Metric 24:	Reporting of Data	High	× 2	2	Data were presented for all outcomes.
Overall Quality Determination‡			~~Medium~~ ⟶ Medium§		~~1.8~~	
Extracted			Yes			

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

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

where High: $\geq$ 1 to $<$ 1.7; Medium: $\geq$ 1.7 to $<$ 2.3; Low: $\geq$ 2.3 to $\leq$ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.
†† This metric met the criteria for high confidence as expected for this type of study.
§ Evaluator's explanation for rating change: "Paper downgraded due to uncertainties in the actual exposure regimen and deviations in the study protocol (e.g., pregnant/postpartum rats were allowed to continue in the study)."

Table 16: **Animal toxicity evaluation results of N-Methylpyrrolidone Producers Group 1997 for a 2-year cancer bioassay study**

Study Citation:	N-Methylpyrrolidone Producers Group (1997). Final report, oncogenicity study with n-methylpyrrolidone (nmp) two-year feeding study in Sprague Dawley rats, with cover letter dated 5/22/1998
Data Type:	2 year cancer bioassay
HERO ID:	4214107

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Identified by structure, nomenclature, CASRN.
	Metric 2:	Test Substance Source	High	× 1	1	Source and production date provided
	Metric 3:	Test Substance Purity	High	× 1	1	Purity such that effects due to test substance.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Concurrent negative controls were used
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive control animals were not required
	Metric 6:	Randomized Allocation	Medium	× 1	2	Computerized stratified randomization used to ensure no body weight differences among the groups
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	High	× 1	1	Preparation and storage were appropriate based on stability analysis
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Diets administered consistently across groups
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Food intake and body weight were monitored in order to calculate daily intakes. Concentrations were analyzed in the diet
	Metric 10:	Exposure Frequency and Duration	Medium	× 1	2	Diets were provided for "approximately 24 months" and were inferred to have been available ad libitum
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	The number of groups and spacing were based on previous repeated dose studies
	Metric 12:	Exposure Route and Method	High	× 1	1	The route and methods were suitable for the test substance
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	All characteristics were reported
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	× 1	1	All conditions were reported
	Metric 15:	Number per Group	High	× 1	1	The number of animals/group was adequate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	Outcomes methodology was reported and sensitive for outcome(s) of interest
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling for outcomes was adequate

Continued on next page . . .

. . . continued from previous page

Study Citation:	N-Methylpyrrolidone Producers Group (1997). Final report, oncogenicity study with n-methylpyrrolidone (nmp) two-year feeding study in Sprague Dawley rats, with cover letter dated 5/22/1998
Data Type:	2 year cancer bioassay
HERO ID:	4214107

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 19:	Blinding of Assessors	Medium	× 1	2	Blinding was not reported for peer-review evaluation of histopathological findings, but this is not expected to impact on the results.
	Metric 20:	Negative Control Response	High	× 1	1	The negative controls responded appropriately
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	No confounding variables were reported
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health outcomes unrelated to exposure were found.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were appropriate for the outcomes
	Metric 24:	Reporting of Data	High	× 2	2	All outcomes were reported
Overall Quality Determination‡			High		1.1	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

5 Genetic toxicity studies

Table 17: **In vitro evaluation results of Mortelmans et al., 1986 for bacterial reverse mutation**

Study Citation:	K. Mortelmans, S. Haworth, T. Lawlor, W. Speck, B. Tainer, E. Zeiger (1986). Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals Environmental Mutagenesis, 8(S7,S7), 1-119
Data Type:	Bacterial reverse mutation for NMP
HERO ID:	7315

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance was reported by name: N-methyl-2-pyrrolidone (NMP), CASRN 872-50-4 in table 1 and by structure in appendix 1
	Metric 2:	Test Substance Source	High	× 1	1	Test substance was obtained from Aldrich, Lot number was not reported, however, the test substance is unlikely to vary in composition
	Metric 3:	Test Substance Purity	High	× 1	1	Test substance purity reported in table 1: vendor purity-99% %, analyzed purity , blank testing lab -EGG
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Concurrent solvent controls were tested with and without metabolic activation. Solvent controls include water, DMSO and ethanol or acetone if not soluble in water or DMSO. The solvent used for the test substance was water reported in appendix 2
	Metric 5:	Positive Controls	High	× 2	2	Positive controls were tested with and without metabolic activation: without metabolic activation: sodium azide for TA1535 and TA100, 4-nitro-o-phenylenediamine for TA98, and 9-aminoacridine for TA97 and TA1537; 2-aminoanthracene was used with all strains with hamster and rat liver metabolic activation systems.
	Metric 6:	Assay Procedures	High	× 1	1	The assay procedure was well described
	Metric 7:	Standards for Tests	Not Rated	NA	NA	Not applicable for this study type
Domain 3: Exposure Characterization						
	Metric 8:	Preparation and Storage of Test Substance	High	× 1	1	Chemical preparation was reported in detail. Chemical was provided with stability and storage conditions, specific storage conditions for the test substance were not reported; however, this is appropriate for the study design (single-dose administration).
	Metric 9:	Consistency of Exposure Administration	High	× 1	1	Administration was consistent across study groups
	Metric 10:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported in table 171 of appendix 2: 0, 100, 333, 1000, 3333, 10000 ug/plate

Continued on next page . . .

. . . continued from previous page

Study Citation: K. Mortelmans, S. Haworth, T. Lawlor, W. Speck, B. Tainer, E. Zeiger (1986). Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals Environmental Mutagenesis, 8(S7,S7), 1-119
Data Type: Bacterial reverse mutation for NMP
HERO ID: 7315

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Number of Exposure Groups and Concentration Spacing	High	× 2	2	Exposure duration was appropriate for the study type and was reported for each part of the procedure: 20 minute pre-incubation and 48 h plate incubation after exposure
	Metric 12:	Exposure Route and Method	High	× 1	1	Number of doses was adequate for the study type. Dose spacing and upper limits were based on solubility and cytotoxicity
	Metric 13:	Metabolic Activation	High	× 1	1	Testing was done in the presence and absence of S9 metabolic activation. Preparation of S9 was reported.
Domain 4: Test Model						
	Metric 14:	Test Model	High	× 2	2	The identity and source of the S. typhimrium strains TA1535, TA1537, TA98, and TA100 were reported and appropriate. These strains are routinely used for the outcome of interest.
	Metric 15:	Number per Group	High	× 1	1	Three plates per dose level were utilized.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	The outcome assessment was appropriate for the outcome of interest
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	The outcome assessment was consistent in protocol and timing across all dose groups
	Metric 18:	Sampling Adequacy	Not Rated	NA	NA	Not applicable for the study type
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Not applicable for the study type
Domain 6: Confounding / Variable Control						
	Metric 20:	Confounding Variables in Test Design and Procedures	High	× 2	2	No confounding variables were reported. The number or organisms was not reported but based on a citation it is assumed to be consistent across doses.
	Metric 21:	Confounding Variables in Outcomes Unrelated to Exposure	High	× 1	1	Data on confounding variables not related to exposure were not reported
Domain 7: Data Presentation and Analysis						
	Metric 22:	Data Analysis	High	× 1	1	Statistical analysis was not conducted, however sufficient data were provided to allow for statistical testing.
	Metric 23:	Data Interpretation	High	× 2	2	Evaluation criteria was cited previously and briefly described and were consistent with established practice
	Metric 24:	Cytotoxicity Data	High	× 1	1	Cytotoxicity testing was reported and used to determine dose range for the test substance

Continued on next page . . .

. . . continued from previous page

Study Citation:	K. Mortelmans, S. Haworth, T. Lawlor, W. Speck, B. Tainer, E. Zeiger (1986). Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals Environmental Mutagenesis, 8(S7,S7), 1-119
Data Type:	Bacterial reverse mutation for NMP
HERO ID:	7315

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 25: Reporting of Data	High	× 2	2	Appendix 2 table 171 reports data as mean SEM for all dose groups. Table 1 includes summary +,-,eq
Overall Quality Determination‡		High		1.0	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 18: **In vitro evaluation results of Wells et al., 1988 for Ames test**

Study Citation:	D. A. Wells, H. F. Thomas, G. A. Digenis (1988). Mutagenicity and cyto-toxicity of n-methyl-2-pyrrolidinone and 4-(methylamino)butanoic acid in the salmonella microsome assay Journal of Applied Toxicology, 8(2,2), 135-139
Data Type:	Ames for NMP
HERO ID:	1459767

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance was identified as N-methyl-2-pyrrolidinone (NMP).
	Metric 2:	Test Substance Source	High	× 1	1	Source of test substance was Aldrich Chemical Co (Milwaukee, WI).
	Metric 3:	Test Substance Purity	High	× 1	1	Test substance is reported to be Gold Label grade.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Sterile distilled water (vehicle) was used as a negative control.
	Metric 5:	Positive Controls	Medium	× 2	4	Positive controls were concurrently run. It was unclear whether each positive control was appropriate for each strain according to current standards and guidelines. Positive control results were not reported.
	Metric 6:	Assay Procedures	Medium	× 1	2	Details regarding the direct plate incorporation and pre-incubation methods were cited to other publications, but the methodology described appeared appropriate and consistent with current standards and guidelines.
	Metric 7:	Standards for Tests	Not Rated	NA	NA	Not applicable for this study.
Domain 3: Exposure Characterization						
	Metric 8:	Preparation and Storage of Test Substance	High	× 1	1	Preparation of test substance was reported. Storage of the test substance was not reported, but this is appropriate given the study design (single-dose administration).
	Metric 9:	Consistency of Exposure Administration	High	× 1	1	Exposures were consistently administered across study groups
	Metric 10:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported without ambiguity.
	Metric 11:	Number of Exposure Groups and Concentration Spacing	High	× 2	2	Exposure duration was appropriate for the pre-incubation assay. The plate incorporation exposure duration was cited to another publication, but was considered to be appropriate given that the publication cited was Maron and Ames 1983.
	Metric 12:	Exposure Route and Method	High	× 1	1	Number of exposure groups was appropriate (six log-linear doses). Cytotoxicity was observed at highest dose.

Continued on next page . . .

. . . continued from previous page

Study Citation: D. A. Wells, H. F. Thomas, G. A. Digenis (1988). Mutagenicity and cyto-toxicity of n-methyl-2-pyrrolidinone and 4-(methylamino)butanoic acid in the salmonella microsome assay Journal of Applied Toxicology, 8(2,2), 135-139
Data Type: Ames for NMP
HERO ID: 1459767

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 13:	Metabolic Activation	High	× 1	1	Exposure were performed in the presence and absence of metabolic activation (S9).
Domain 4: Test Model						
	Metric 14:	Test Model	Medium	× 2	4	Test strains were described; however, limited descriptive information were provided.
	Metric 15:	Number per Group	Medium	× 1	2	The number of replicates per group is unclear. Figure legends for both the direct plate incorporation assay (Figure 1) and the pre-incubation assay (Figure 2) report n = 8 "obtained from pooled data from two independent experiments." In the methods describing the direct plate incorporation test, it was reported that n = 4 plates/dose and "each experiment was repeated once." In the methods describing the pre-incubation test, it was implied but not explicitly stated that n = 3. Despite this uncertainty, n = 3 replicates per dose level is considered adequate for the outcome of interest, so this deficiency i s not expected to have substantially affected results.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	The assessment methodology is appropriate for the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	Low	× 1	3	It was reported that "revertant colonies were counted manually [...] or with a Biotran II automated colony counter." It is not clear which treatment groups were assessed manually or automatically. This is considered to be a significant inconsistency that may have substantially impacted results.
	Metric 18:	Sampling Adequacy	Not Rated	NA	NA	Not applicable for this study.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Not applicable for thi
Domain 6: Confounding / Variable Control						
	Metric 20:	Confounding Variables in Test Design and Procedures	Low	× 2	6	Information on potential confounding variables were not reported.
	Metric 21:	Confounding Variables in Outcomes Unrelated to Exposure	Medium	× 1	2	Data on outcomes unrelated to exposure were not reported.
Domain 7: Data Presentation and Analysis						
	Metric 22:	Data Analysis	High	× 1	1	Data were analyzed by Bonferroni t-test of differences between means of the treatment dose vs control. P=0.05
	Metric 23:	Data Interpretation	High	× 2	2	Data interpretation was consistent with standards.

Continued on next page . . .

. . . continued from previous page

Study Citation:	D. A. Wells, H. F. Thomas, G. A. Digenis (1988). Mutagenicity and cyto-toxicity of n-methyl-2-pyrrolidinone and 4-(methylamino)butanoic acid in the salmonella microsome assay Journal of Applied Toxicology, 8(2,2), 135-139
Data Type:	Ames for NMP
HERO ID:	1459767

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 24: Cytotoxicity Data	High	× 1	1	Cytotoxic endpoints were described.
	Metric 25: Reporting of Data	Low	× 2	6	Although the direct plate incorporation method was carried out for strains TA97, TA98, TA100, TA102, TA104, TA2638, UTH8413, and UTH8414, and the pre-incubation method was carried out for strains TA98 and TA104, only a small subset of these results are reported quantitatively. It is unclear why the remainder of the results were not reported quantitatively.
Overall Quality Determination‡		High		1.5	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 19: **In vitro evaluation results of Wells et al., 1988 for Ames test with N-MeGABA**

Study Citation:	D. A. Wells, H. F. Thomas, G. A. Digenis (1988). Mutagenicity and cyto-toxicity of n-methyl-2-pyrrolidinone and 4-(methylamino)butanoic acid in the salmonella microsome assay Journal of Applied Toxicology, 8(2,2), 135-139
Data Type:	Ames with N-MeGABA
HERO ID:	1459767

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance was identified as 4-(methylamino)butanoic acid (N-MeGABA).
	Metric 2:	Test Substance Source	Low	× 1	3	Test substance was synthesized by authors. Analytical confirmation was not reported.
	Metric 3:	Test Substance Purity	Low	× 1	3	Purity of test substance was not reported.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Sterile distilled water (vehicle) was used as a negative control.
	Metric 5:	Positive Controls	Medium	× 2	4	Positive controls were concurrently run. It was unclear whether each positive control was appropriate for each strain according to current standards and guidelines. Positive control results were not reported.
	Metric 6:	Assay Procedures	Medium	× 1	2	Details regarding the direct plate incorporation and pre-incubation methods were cited to other publications, but the methodology described appeared appropriate and consistent with current standards and guidelines.
	Metric 7:	Standards for Tests	Not Rated	NA	NA	Not applicable for this study.
Domain 3: Exposure Characterization						
	Metric 8:	Preparation and Storage of Test Substance	High	× 1	1	Preparation of test substance was reported. Storage of the test substance was not reported, but this is appropriate given the study design (single-dose administration).
	Metric 9:	Consistency of Exposure Administration	High	× 1	1	Exposures were consistently administered across study groups
	Metric 10:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported without ambiguity.
	Metric 11:	Number of Exposure Groups and Concentration Spacing	High	× 2	2	Exposure duration was appropriate for the pre-incubation assay. The plate incorporation exposure duration was cited to another publication, but was considered to be appropriate given that the publication cited was Maron and Ames 1983.
	Metric 12:	Exposure Route and Method	High	× 1	1	Number of exposure groups was appropriate (six log-linear doses). Cytotoxicity was observed at highest dose. This highest dose was selected based on solubility limits.

Continued on next page . . .

. . . continued from previous page

Study Citation: D. A. Wells, H. F. Thomas, G. A. Digenis (1988). Mutagenicity and cyto-toxicity of n-methyl-2-pyrrolidinone and 4-(methylamino)butanoic acid in the salmonella microsome assay Journal of Applied Toxicology, 8(2,2), 135-139
Data Type: Ames with N-MeGABA
HERO ID: 1459767

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Metabolic Activation	High	× 1	1	Exposure were performed in the presence and absence of metabolic activation (S9).
Domain 4: Test Model						
	Metric 14:	Test Model	Medium	× 2	4	Test strains were described; however, limited descriptive information were provided.
	Metric 15:	Number per Group	Medium	× 1	2	The number of replicates per group is unclear. Figure legends for both the direct plate incorporation assay (Figure 1) and the pre-incubation assay (Figure 2) report n = 8 "obtained from pooled data from two independent experiments". In the methods describing the direct plate incorporation test, it was reported that n = 4 plates/dose and "each experiment was repeated once". In the methods describing the pre-incubation test, it was implied but not explicitly stated that n = 3. Despite this uncertainty, n = 3 replicates per dose level is considered adequate for the outcome of interest, so this deficiency is not expected to have substantially affected results.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	The assessment methodology is appropriate for the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	Low	× 1	3	It was reported that "revertant colonies were counted manually [...] or with a Biotran II automated colony counter." It is not clear which treatment groups were assessed manually or automatically. This is considered to be a significant inconsistency that may have substantially impacted results.
	Metric 18:	Sampling Adequacy	Not Rated	NA	NA	Not applicable for this study.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Not applicable for this study.
Domain 6: Confounding / Variable Control						
	Metric 20:	Confounding Variables in Test Design and Procedures	Low	× 2	6	Information on potential confounding variables were not reported.
	Metric 21:	Confounding Variables in Outcomes Unrelated to Exposure	Medium	× 1	2	Data on outcomes unrelated to exposure were not reported.
Domain 7: Data Presentation and Analysis						
	Metric 22:	Data Analysis	High	× 1	1	Data were analyzed by Bonferroni t-test of differences between means of the treatment dose vs control. P=0.05
	Metric 23:	Data Interpretation	High	× 2	2	Data interpretation was consistent with standards.

Continued on next page . . .

. . . continued from previous page

Study Citation:	D. A. Wells, H. F. Thomas, G. A. Digenis (1988). Mutagenicity and cyto-toxicity of n-methyl-2-pyrrolidinone and 4-(methylamino)butanoic acid in the salmonella microsome assay Journal of Applied Toxicology, 8(2,2), 135-139
Data Type:	Ames with N-MeGABA
HERO ID:	1459767

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 24: Cytotoxicity Data	High	× 1	1	Cytotoxic endpoints were described.
	Metric 25: Reporting of Data	Low	× 2	6	Although the direct plate incorporation method was carried out for strains TA97, TA98, TA100, TA102, TA104, TA2638, UTH8413, and UTH8414, and the pre-incubation method was carried out for strains TA98 and TA104, only a small subset of these results are reported quantitatively. It is unclear why the remainder of the results were not reported quantitatively.
Overall Quality Determination‡		High		1.7	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 20: **Animal toxicity evaluation results of Engelhardt and Fleig 1993 for micronucleus and chromosomal aberrations assays**

Study Citation:	G. Engelhardt, H. Fleig (1993). 1-Methyl-2-pyrrolidinone (NMP) does not induce structural and numerical chromosomal aberrations in vivo Mutation Research, 298(3,3), 149-155
Data Type:	Micronucleus and chromosomal aberrations assays for NMP
HERO ID:	3539781

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance was clearly identified by name (1-methyl-2-pyrrolidinone; NMP). A CASRN was also provided (872-50-4).
	Metric 2:	Test Substance Source	High	× 1	1	The source of the test substance (a manufacturer) was reported. Although a lot/batch number was not reported, the test substance is not expected to vary in composition.
	Metric 3:	Test Substance Purity	High	× 1	1	The purity of the test substance was reported (>99.8%). Any observed effects are likely due to the test substance itself.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	The study authors reported using an appropriate concurrent negative control groups (vehicle-only was clearly specified).
	Metric 5:	Positive Controls	High	× 1	1	Positive controls were run concurrently. In both assays, cyclophosphamide was used as a positive control for clastogenic activity and vincristine sulfate was used as a positive control for spindle poison effects. Benomyl was used in the micronucleus test only, Although fewer animals/group were used for these substances (2 to 3 animals/sex), significant positive responses were observed.
	Metric 6:	Randomized Allocation	High	× 1	1	The study indicated that animals were randomly assigned to test groups (separately according to sex).
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Medium	× 1	2	The test substance preparation (i.e., dissolved in distilled water) and storage conditions (i.e., kept at 4 to 6 degrees C under N2 conditions) were reported.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Exposures were administered consistently across study groups. Gavage volumes were consistent throughout (10 mL/kg).
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported without ambiguity (methods section and data tables).
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	The test substance was administered as a single dose via gavage; this treatment is adequate for the study types/outcomes of interest.

Continued on next page . . .

. . . continued from previous page

Study Citation:	G. Engelhardt, H. Fleig (1993). 1-Methyl-2-pyrrolidinone (NMP) does not induce structural and numerical chromosomal aberrations in vivo Mutation Research, 298(3,3), 149-155
Data Type:	Micronucleus and chromosomal aberrations assays for NMP
HERO ID:	3539781

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Number of Exposure Groups and Dose Spacing	Medium	× 1	2	The number of dose groups was specified (3 plus negative controls for the micronucleus assay and 2 plus negative controls for the chromosomal aberrations assay); the number of groups used in the chromosomal assay was fewer than recommended by study type. The highest dose was justified by the authors as 80% of the LD50.
	Metric 12:	Exposure Route and Method	High	× 1	1	The route and of exposure was reported (oral gavage) and was suited to the test substance.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	Minor uncertainties in the reporting of test animal characteristics (health status, and age) are unlikely to have a substantial impact on results. The test animals were obtained from a commercial source. The test species used for the micronucleus assay (mice) was appropriate for the outcome of interest. Hamsters were used for the chromosomal aberrations assay; the use of this rodent species was not justified in the study report.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	× 1	3	Husbandry conditions were not sufficiently reported to evaluate if husbandry was adequate and if differences occurred between control and exposed populations.
	Metric 15:	Number per Group	High	× 1	1	The number of animals per study group was reported (i.e., 5/sex/time point) and appropriate for the study type/outcome analysis.
Domain 5: Outcome Assessment						

Continued on next page . . .

. . . continued from previous page

Study Citation:	G. Engelhardt, H. Fleig (1993). 1-Methyl-2-pyrrolidinone (NMP) does not induce structural and numerical chromosomal aberrations in vivo Mutation Research, 298(3,3), 149-155
Data Type:	Micronucleus and chromosomal aberrations assays for NMP
HERO ID:	3539781

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 16:	Outcome Assessment Methodology	Low	× 2	6	The outcome assessment methodology was described; some details (bone marrow and slide prep for micronuclei and analysis of chromosomal aberrations) were cited to other publications. In the micronucleus assay, outcomes were evaluated 16, 24, and 48 hours after dosing at the high-dose (only at 24 hours for the remaining two doses); at least two time points, no sooner than 24 hours and up to 48 hours, is recommended by guideline after a single treatment. With respect to chromosomal aberrations, the methods indicate that metaphases were analyzed 24 and 48 hours after dosing at the high-dose (only at 24 hours for the low-dose). However, the data table shows sacrifice intervals of 16 and 24 hours, and at least two time points (12 to 18 hours after dosing and up to 24 hours later) are recommended by the study type.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently across study groups.
	Metric 18:	Sampling Adequacy	Medium	× 1	2	Sampling for micronuclei was 1000 erythrocytes/animal (500 recommended by study type); however, only 100 metaphases/animal were evaluated for chromosomal aberrations (200 metaphases recommended by study type).
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	This metric was not applicable to the study type (blinding was not reported).
	Metric 20:	Negative Control Response	High	× 1	1	The biological responses of the negative control groups were adequate (low incidences of micronuclei/chromosomal aberrations).
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	× 2	6	Information on potential confounding variables were not reported. Only the mean body weight of animals per assay was reported (29.9 g for mice and 25.9 g for hamsters).
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	× 1	3	Data on health outcomes unrelated to exposure were not reported.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistics were not reported in the methods; however, Tables 2 and 3 indicate that data were analyzed using Fisher's exact test. For the micronuclei assay, data for individual animals was provided, allowing for independent analyses.

Continued on next page . . .

. . . continued from previous page

Study Citation:	G. Engelhardt, H. Fleig (1993). 1-Methyl-2-pyrrolidinone (NMP) does not induce structural and numerical chromosomal aberrations in vivo Mutation Research, 298(3,3), 149-155
Data Type:	Micronucleus and chromosomal aberrations assays for NMP
HERO ID:	3539781

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 24: Reporting of Data	High	× 2	2	All exposure-related data (by dose group, sex, and time point) were presented in Tables 2 and 3.
Overall Quality Determination‡		High		1.6	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

6 Developmental and Reproductive

Table 21: **Animal toxicity evaluation results of Lee et al., 1987 for an inhalation developmental study on growth (early life) and development outcomes**

Study Citation:	Lee, KP; Chromey, NC; Culik, R; Barnes, JR; Schneider, PW (1987). Toxicity of N-methyl-2-pyrrolidone (NMP): Teratogenic, subchronic, and two-year inhalation studies Fundamental and Applied Toxicology, 9(2), 222-235
Data Type:	
HERO ID:	3539878

Domain	Metric		Rating†	MWF*	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Chemical structure, established nomenclature, and physiochemical properties were reported
	Metric 2:	Test Substance Source	Medium	× 1	2	The source was not reported. However, the concentration of exposures were measured by IR spectrometry and gas chromatography.
	Metric 3:	Test Substance Purity	Medium	× 1	2	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.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	A concurrent control group was included
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls not required
	Metric 6:	Randomized Allocation	Medium	× 1	2	"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."
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	High	× 1	1	Aerosol generation system was described and appropriate.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Exposures were consistent across groups
	Metric 9:	Reporting of Doses/Concentrations	Low	× 2	6	The particle size distribution was not determined and there was uncertainty about whether analytical or nominal concentration was reported.

Continued on next page . . .

. . . continued from previous page

Study Citation: Lee, KP; Chromey, NC; Culik, R; Barnes, JR; Schneider, PW (1987). Toxicity of N-methyl-2-pyrrolidone (NMP): Teratogenic, subchronic, and two-year inhalation studies Fundamental and Applied Toxicology, 9(2), 222-235

Data Type:

HERO ID: 3539878

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Exposed GD6-15 for 6 h/day
	Metric 11:	Number of Exposure Groups and Dose Spacing	Medium	× 1	2	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.
	Metric 12:	Exposure Route and Method	High	× 1	1	Dynamic chambers were used
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	Age and overall health status were not reported
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	× 1	3	Husbandry was not adequately reported.
	Metric 15:	Number per Group	High	× 1	1	The number of animals/group was sufficient for outcome analysis
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	The outcomes of interest were addressed by the methodology
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently.
	Metric 18:	Sampling Adequacy	High	× 1	1	Adequate sampling for the outcomes of interest was conducted
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Subjective outcomes were not assessed
	Metric 20:	Negative Control Response	High	× 1	1	Negative controls responded appropriately
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	× 2	4	No confounding variables were reported. However, NMP is an irritant. Breathing rates and body temperature measurements were not made to rule our reflex bradypnea.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	× 1	2	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.
Domain 7: Data Presentation and Analysis						

Continued on next page . . .

. . . continued from previous page

Study Citation:	Lee, KP; Chromey, NC; Culik, R; Barnes, JR; Schneider, PW (1987). Toxicity of N-methyl-2-pyrrolidone (NMP): Teratogenic, subchronic, and two-year inhalation studies Fundamental and Applied Toxicology, 9(2), 222-235
Data Type:	
HERO ID:	3539878

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 23: Statistical Methods	High	× 1	1	The described statistical methods were appropriate
	Metric 24: Reporting of Data	High	× 2	2	Data were reported for outcomes
Overall Quality Determination‡		High		1.5	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 22: **Animal toxicity evaluation results of Sitarek et al., 2008 for a reproductive-male study on reproductive outcomes**

Study Citation:	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					
Data Type:	Reproductive-males					
HERO ID:	3540734					
Domain		Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	The test substance was identified by name and CASRN.
	Metric 2:	Test Substance Source	Medium	× 1	2	Source identified by name.
	Metric 3:	Test Substance Purity	Low	× 1	3	Purity not reported. Analytical grade test substance used.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Concurrent negative control animals were included.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive control animals not required.
	Metric 6:	Randomized Allocation	Low	× 1	3	Method of randomization for animal allocation was not reported.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Low	× 1	3	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.
	Metric 8:	Consistency of Exposure Administration	Low	× 1	3	It is unclear whether doses were administered consistently, as dosing volumes were not reported.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Frequency and duration were reported.
	Metric 11:	Number of Exposure Groups and Dose Spacing	Medium	× 1	2	No justification provided for the number of groups and dose spacing.
	Metric 12:	Exposure Route and Method	High	× 1	1	The route and method were appropriate.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	The source, species, strain, sex, and age were reported. Initial body weight and health status were not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	× 1	2	All husbandry conditions except air changes were reported.
	Metric 15:	Number per Group	High	× 1	1	The number per group was appropriate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	Outcome assessment methodology was reported.

Continued on next page . . .

. . . continued from previous page

Study Citation:	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
Data Type:	Reproductive-males
HERO ID:	3540734

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding not required.
	Metric 20:	Negative Control Response	High	× 1	1	Negative control responses were adequate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	No confounding variables were observed.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health outcomes unrelated to exposure were reported.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical analysis was described and appropriate.
	Metric 24:	Reporting of Data	Low	× 2	6	Data were presented, but severity and incidence data for histopathological findings were not included.
Overall Quality Determination‡			High		1.6	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 23: **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 Citation:	Saillenfait, AM; Gallissot, F; Langonné, I; Sabaté, JP (2002). Developmental toxicity of N-methyl-2-pyrrolidone administered orally to rats Food and Chemical Toxicology, 40(11), 1705-1712
Data Type:	Oral developmental rat, maternal effects
HERO ID:	3551103

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	Medium	× 2	4	Test substance identified by name only.
	Metric 2:	Test Substance Source	Medium	× 1	2	Source identified by name.
	Metric 3:	Test Substance Purity	High	× 1	1	The reported purity was such that effects likely due to the test substance.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Concurrent negative controls were included.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls not required.
	Metric 6:	Randomized Allocation	Medium	× 1	2	Stratified randomization was used so mean body weights were similar among groups on gestation day 0.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Medium	× 1	2	limited details on preparation were reported. Frequency of preparation and storage were not reported.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Exposures were administered consistently.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Frequency and duration were reported.
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	The number of groups and spacing were based on dose-range finding studies.
	Metric 12:	Exposure Route and Method	High	× 1	1	The route and method were appropriate.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	The source, species, strain, sex, and initial body weight were reported. Health status and age were not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	× 1	2	All husbandry conditions were reported except room air changes were reported.
	Metric 15:	Number per Group	High	× 1	1	The number of dams per group was appropriate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	Outcome assessment methodology was appropriate.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Saillenfait, AM; Gallissot, F; Langonné, I; Sabaté, JP (2002). Developmental toxicity of N-methyl-2-pyrrolidone administered orally to rats Food and Chemical Toxicology, 40(11), 1705-1712
Data Type:	Oral developmental rat, maternal effects
HERO ID:	3551103

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding not applicable.
	Metric 20:	Negative Control Response	High	× 1	1	Negative control responses were appropriate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	No confounding variables were reported.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health outcomes unrelated to exposure were observed.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical analysis was conducted and appropriate.
	Metric 24:	Reporting of Data	High	× 2	2	Data were reported for all outcomes.
Overall Quality Determination‡			High		1.3	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 24: **Animal toxicity evaluation results of Saillenfait et al., 2003 for inhalation study on developmental and reproductive outcomes**

Study Citation:	Saillenfait, AM; 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					
Data Type:						
HERO ID:	3551104					
Domain		Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Nomenclature and CASRN were reported
	Metric 2:	Test Substance Source	High	× 1	1	Source reported
	Metric 3:	Test Substance Purity	High	× 1	1	Purity (99.5%) such that effects likely due to test substance
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Concurrent negative control animals were included
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls were not required
	Metric 6:	Randomized Allocation	High	× 1	1	Females were randomly assigned to exposure groups
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Medium	× 1	2	Method of generation and equipment used were reported; however, storage was not.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Exposures were administered consistently
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Target and analytical concentrations were reported. The analytical method was reported and appropriate.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Exposures occurred 6 hr/d on GD 6-20.
	Metric 11:	Number of Exposure Groups and Dose Spacing	Medium	× 1	2	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.
	Metric 12:	Exposure Route and Method	Low	× 1	3	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.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	Age, and health status were not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	× 1	1	Husbandry conditions were reported and appropriate.

Continued on next page . . .

. . . continued from previous page

Study Citation: Saillenfait, AM; 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
Data Type:
HERO ID: 3551104

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Number per Group	High	× 1	1	The number of females/group 25-26 was appropriate for the study type and outcomes.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	Low	× 2	6	Outcome assessment methodology for maternal and fetal evaluations addressed the outcomes of interest; however, breathing rate/body temperature was not measured.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcome assessment was carried out consistently among groups
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling details were reported and were adequate
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	No subjective outcomes were assessed.
	Metric 20:	Negative Control Response	High	× 1	1	Negative control responses were appropriate
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	× 2	6	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.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health differences unrelated to exposure were reported
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were described and appropriate for the dataset
	Metric 24:	Reporting of Data	High	× 2	2	Data for all outcomes were reported.
Overall Quality Determination‡			High		1.5	
Extracted			Yes			

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

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

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

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

Table 25: **Animal toxicity evaluation results of Exxon 1992 for a developmental toxicity study in rats on growth (early life) and development outcomes**

Study Citation:	ISP (1992). Initial submission: Developmental toxicity study in rats with n-methylpyrrolidone (draft report) with attachments and cover letter dated 041092
Data Type:	Developmental toxicity study in rats
HERO ID:	3563347

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	Medium	× 2	4	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.
	Metric 2:	Test Substance Source	Medium	× 1	2	The batch number was provided. The source was of the test substance was not provided but reported as sponsor.
	Metric 3:	Test Substance Purity	Medium	× 1	2	The purity was assumed to be 100%, however no data was provided for support.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	A concurrent vehicle control was included.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls were not required.
	Metric 6:	Randomized Allocation	Medium	× 1	2	Method of allocation was based on confirmed mating.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	High	× 1	1	Test substance preparation and storage were reported. Stability and concentration were reported.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Doses were administered consistently.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Duration and frequency were reported.
	Metric 11:	Number of Exposure Groups and Dose Spacing	Medium	× 1	2	The number of groups and spacing were not justified but were sufficient to show results relevant to the outcome of interest.
	Metric 12:	Exposure Route and Method	High	× 1	1	The exposure route and method were appropriate.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	The source, species, strain, sex, health status, and initial body weight were reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	× 1	1	All husbandry conditions were reported.
	Metric 15:	Number per Group	High	× 1	1	The number of animals per group was appropriate.
Domain 5: Outcome Assessment						

Continued on next page . . .

. . . continued from previous page

Study Citation:	ISP (1992). Initial submission: Developmental toxicity study in rats with n-methylpyrrolidone (draft report) with attachments and cover letter dated 041092
Data Type:	Developmental toxicity study in rats
HERO ID:	3563347

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	Outcome assessment methodology was described and appropriate.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcome assessment was consistent.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding not required in this assay.
	Metric 20:	Negative Control Response	High	× 1	1	Negative control responses were appropriate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	× 2	4	Distribution by mating confirmation resulted in 4 non-pregnant control animals, but there were a sufficient number of offspring available for comparison.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health outcomes unrelated to exposure were observed.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were well described and appropriate.
	Metric 24:	Reporting of Data	High	× 2	2	Data were reported for all outcomes.
Overall Quality Determination‡			High		1.3	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 26: **Animal toxicity evaluation results of Solomon et al., 1995 for a 2-generation reproduction/developmental study, inhalation study on reproductive, and growth (early life) and development outcomes**

Study Citation:	Solomon, HM; Burgess, BA; Kennedy, GL, Jr; Staples, RE (1995). 1-methyl-2-pyrrolidone (NMP): Reproductive and developmental toxicity study by inhalation in the rat Drug and Chemical Toxicology, 18(4), 271-293					
Data Type:	2-generation reproduction/developmental study, inhalation					
HERO ID:	2761868					
Domain		Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Clearly identified
	Metric 2:	Test Substance Source	Medium	× 1	2	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.
	Metric 3:	Test Substance Purity	High	× 1	1	Purity reported (99.9%). Impurities were identified and present in quantities that would not influence the results.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	A concurrent negative control was used and appears to be sham- exposed.
	Metric 5:	Positive Controls	Not Rated	NA	NA	this metric is not rated/applicable for this study type.
	Metric 6:	Randomized Allocation	High	× 1	1	Rats were distributed randomly into control and treated groups using a randomized block design based on body weight.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	High	× 1	1	The test substance preparation, method, and equipment used to generate the vapor were reported and appropriate.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Details of exposure administration were reported and administered consistently across study groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	× 2	4	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).
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	The exposure frequency and duration of exposure were appropriately identified.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Solomon, HM; Burgess, BA; Kennedy, GL, Jr; Staples, RE (1995). 1-methyl-2-pyrrolidone (NMP): Reproductive and developmental toxicity study by inhalation in the rat Drug and Chemical Toxicology, 18(4), 271-293
Data Type:	2-generation reproduction/developmental study, inhalation
HERO ID:	2761868

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Number of Exposure Groups and Dose Spacing	Medium	× 1	2	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.
	Metric 12:	Exposure Route and Method	Medium	× 1	2	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.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	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.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	× 1	1	All husbandry conditions were reported, were adequate, and were the same for control and exposed groups.
	Metric 15:	Number per Group	High	× 1	1	The number of animals per study group was reported and appropriate for the study type and outcome analysis.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	The outcome assessment methodology was reported and addressed the intended outcomes of interest.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Details of the outcome assessment protocol were reported and outcomes were assessed consistently across study groups.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was reported and adequate for the outcomes of interest.
	Metric 19:	Blinding of Assessors	High	× 1	1	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.
	Metric 20:	Negative Control Response	High	× 1	1	The biological responses of the negative control groups were adequate.
Domain 6: Confounding / Variable Control						

Continued on next page . . .

. . . continued from previous page

Study Citation:	Solomon, HM; Burgess, BA; Kennedy, GL, Jr; Staples, RE (1995). 1-methyl-2-pyrrolidone (NMP): Reproductive and developmental toxicity study by inhalation in the rat Drug and Chemical Toxicology, 18(4), 271-293
Data Type:	2-generation reproduction/developmental study, inhalation
HERO ID:	2761868

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	× 2	4	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.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	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.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were clearly described and appropriate.
	Metric 24:	Reporting of Data	High	× 2	2	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.
Overall Quality Determination‡			High		1.2	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 27: **Animal toxicity evaluation results of Intl Specialty 1979 for dermal developmental, offspring and maternal effects study on growth (early life) and development outcomes**

Study Citation:	(1992). Initial submission: teratologic dose range-finding study w/ n-methylpyrrolidone in sprague dawley rats with cover letter dated 09/01/92
Data Type:	Dermal developmental, offspring and maternal effects
HERO ID:	3564297

Domain		Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	Medium	× 2	4	Test substance identified by name.
	Metric 2:	Test Substance Source	Low	× 1	3	Sponsor (GAF Corp) was identified as the source of the test substance.
	Metric 3:	Test Substance Purity	High	× 1	1	Purity such that effects due to test substance.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Concurrent negative controls were used.
	Metric 5:	Positive Controls	High	× 1	1	Concurrent positive controls were used.
	Metric 6:	Randomized Allocation	Medium	× 1	2	Animals allocated by random number assignment sheet.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Low	× 1	3	Preparation and storage were not reported.
	Metric 8:	Consistency of Exposure Administration	Low	× 1	3	Test material was rubbed into the skin. Dosing volume, diluent or dilution factor were not described. It is unclear whether doses were administered consistently.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Exposure duration and frequency were reported.
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	The number of groups and dose spacing were reported and justified.
	Metric 12:	Exposure Route and Method	High	× 1	1	The route and method of exposure were appropriate.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	The source, strain, sexual state, sex, and initial body weight were reported. Health status and specific numeric age were not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	× 1	2	Temperature, lighting, and humidity were not reported.
	Metric 15:	Number per Group	High	× 1	1	The number of animals per group was appropriate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	Medium	× 2	4	Treatment did not extend throughout the period of organogenesis.

Continued on next page . . .

. . . continued from previous page

Study Citation:	(1992). Initial submission: teratologic dose range-finding study w/ n-methylpyrrolidone in sprague dawley rats with cover letter dated 09/01/92
Data Type:	Dermal developmental, offspring and maternal effects
HERO ID:	3564297

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate for the outcomes of interest.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding was not required.
	Metric 20:	Negative Control Response	High	× 1	1	Negative control responses were appropriate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	No confounding variables in test design and procedures were noted.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health outcomes unrelated to exposures were observed.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were described and appropriate.
	Metric 24:	Reporting of Data	High	× 2	2	Data were presented for all outcomes.
Overall Quality Determination‡			High		1.5	
Extracted			No			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 28: **Animal toxicity evaluation results of Exxon Biomedical 1991 for a multigeneration reproductive toxicity study on rats – reproductive, growth (early life) and developmental outcomes**

Study Citation:	Exxon Biomedical (1991). Multigeneration Rat Reproduction Study with N-Methylpyrrolidone, Project Number 236535					
Data Type:	Multi-generation reproduction study in rats					
HERO ID:	3809420					
Domain		Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	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.
	Metric 2:	Test Substance Source	Medium	× 1	2	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 references a certificate of analysis, it was not included in the study report (i.e., not found in an appendix).
	Metric 3:	Test Substance Purity	Medium	× 1	2	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.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	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).
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive control not indicated by study type.
	Metric 6:	Randomized Allocation	High	× 1	1	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).
Domain 3: Exposure Characterization						

Continued on next page . . .

. . . continued from previous page

Study Citation: Exxon Biomedical (1991). Multigeneration Rat Reproduction Study with N-Methylpyrrolidone, Project Number 236535
Data Type: Multi-generation reproduction study in rats
HERO ID: 3809420

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Preparation and Storage of Test Substance	High	× 1	1	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.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	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).
	Metric 9:	Reporting of Doses/Concentrations	Medium	× 2	4	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 pre-mating 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.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	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.
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	The target doses were based on data for a previously conducted dose-probe study. The high-dose was sufficient t o i nduce t reatment-related e ffects (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).

Continued on next page . . .

. . . continued from previous page

Study Citation: Exxon Biomedical (1991). Multigeneration Rat Reproduction Study with N-Methylpyrrolidone, Project Number 236535
Data Type: Multi-generation reproduction study in rats
HERO ID: 3809420

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 12:	Exposure Route and Method	High	× 1	1	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.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	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).
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	× 1	2	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.
	Metric 15:	Number per Group	High	× 1	1	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).
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	Medium	× 2	4	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.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	The timing/methods of outcome assessments were reported, and appeared to be consistent across treatment groups.

Continued on next page . . .

. . . continued from previous page

Study Citation: Exxon Biomedical (1991). Multigeneration Rat Reproduction Study with N-Methylpyrrolidone, Project Number 236535
Data Type: Multi-generation reproduction study in rats
HERO ID: 3809420

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 18:	Sampling Adequacy	Medium	× 1	2	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).
	Metric 19:	Blinding of Assessors	High	× 1	1	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.
	Metric 20:	Negative Control Response	High	× 1	1	The biological responses of the negative control group were adequate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	There were no significant differences among study groups with respect to initial body weights or food consumption rates.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	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).
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	Low	× 1	3	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).

Continued on next page . . .

. . . continued from previous page

Study Citation:	Exxon Biomedical (1991). Multigeneration Rat Reproduction Study with N-Methylpyrrolidone, Project Number 236535
Data Type:	Multi-generation reproduction study in rats
HERO ID:	3809420

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 24: Reporting of Data	Medium	× 2	4	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.
Overall Quality Determination‡		High		1.4	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 29: **Animal toxicity evaluation results for NMP Producers Group 1999 for a 2-generation dietary reproductive toxicity study in Sprague Dawley rats**

Study Citation:	NMP Producers Group (1999). Two Generation Reproduction Toxicity Study with N-Methylpyrrolidone (NMP) in Sprague Dawley Rats - Administration in the Diet					
Data Type:	2-gen dietary repro tox study in SD rats					
HERO ID:	3809436					
Domain		Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	The test substance was identified as N-methylpyrrolidone (NMP); CAS 872-50-4
	Metric 2:	Test Substance Source	High	× 1	1	The commercial source of the test substance was identified (BASF Aktiengesellschaft). The product number and batch/lot number were reported (Tank 3226-02-97)
	Metric 3:	Test Substance Purity	High	× 1	1	The purity of the test substance was "considered 100%"; An analytical report was included in the appendix and the purity of the test material determined pretest, at 6 and 12 months was 97.3%, 98.5%,and 97.5% respectively.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	An untreated diet control (basal diet only)
	Metric 5:	Positive Controls	Not Rated	NA	NA	No positive control was used; however, is not necessary for this study type.
	Metric 6:	Randomized Allocation	High	× 1	1	Parental Rats were randomly allocated into study group; a computerized randomization program was used and accounted for comparable body weight means. F1 parental generation were chosen at random using a random numbers table. Litters were culled to no more than ten pups using a computerized randomization selection process.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	High	× 1	1	The test substance preparation and storage conditions were reported and appropriate for the test substance. Test diets were prepared every 6 days. Homogeneity was analyzed. NMP is reported as stable in the diet for 32 days at room temperature at the tested concentrations.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Details of exposure administration were reported and appear to be administered consistently across study groups.

Continued on next page . . .

. . . continued from previous page

Study Citation:	NMP Producers Group (1999). Two Generation Reproduction Toxicity Study with N-Methylpyrrolidone (NMP) in Sprague Dawley Rats - Administration in the Diet
Data Type:	2-gen dietary repro tox study in SD rats
HERO ID:	3809436

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Parental P1 and F1 Parental Administered dietary doses were reported without ambiguity. Dietary NMP concentrations were adjusted weekly based on mean body weight and food consumption measurements from the previous week.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Exposure frequency and duration were appropriate for this endpoint; continuously in the diet without restriction, 7 d/wk
	Metric 11:	Number of Exposure Groups and Dose Spacing	Medium	× 1	2	The number of exposure groups and spacing were justified by the study authors (based on a previously conducted 2-generation reproduction toxicity study). Initially, P1 rats were treated with 0, 50, 160, or 500 mg/kg/day. After day 126, the high dose level was reduced to 350 mg/kg/day due to excessive pup mortality in F1a pups; thereafter, the administered high dose level was 350 mg/kg/day for the remainder of the P1 generation exposure. F1 rats were administered 0, 50, 160, and 350 mg/kg/day. The dose spacing was appropriate to evaluate the dose-response relationship
	Metric 12:	Exposure Route and Method	High	× 1	1	The route or method of exposure was reported and suited to the test substance; administered orally via the diet.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	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 (Charles River Laboratories). The test species and strain were an appropriate animal model for the evaluation of the specific outcome(s) of interest (e.g., routinely used for similar study types and consistent with OECD TG 416).
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	× 1	1	All husbandry conditions were reported and adequate. Conditions were the same for control and exposed population
	Metric 15:	Number per Group	High	× 1	1	The number of animals per study group was reported (30 sex/dose in P1 and F1 generations), appropriate for the study type and outcome analysis.
Domain 5: Outcome Assessment						

Continued on next page . . .

. . . continued from previous page

Study Citation: NMP Producers Group (1999). Two Generation Reproduction Toxicity Study with N-Methylpyrrolidone (NMP) in Sprague Dawley Rats - Administration in the Diet
Data Type: 2-gen dietary repro tox study in SD rats
HERO ID: 3809436

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	The outcome assessment methodologies were appropriate for the endpoints of interest and were generally consistent with OECD test guidelines for two-generation reproduction testing (OECD TG 416).
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Details of the outcome assessment protocol were reported and were assessed consistently across study groups. The rest period between F1a and F1b litters was shortened as compared to the rest period specified in the protocol and feed consumption was not measured prior to the mating period for the F1b litter due to the time constraint. The shortening of the rest period is not likely to adversely affect the outcome assessment.
	Metric 18:	Sampling Adequacy	High	× 1	1	Details regarding sampling for the outcomes of interest were reported and the study used adequate sampling for the outcomes of interest
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Not applicable for this study type
	Metric 20:	Negative Control Response	High	× 1	1	The biological responses of the negative control group were reported and were adequate
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	There were no differences among the study groups in initial body weight (individual wt of P1 animals was not > 20% of the mean bd wt for each sex in each group). Food consumption was reported; palatability issues were not noted.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	Viability exams and clinical observations were conducted for all study groups; it was noted that there was a low incidence of sporadically occurring common laboratory health issues in all treatment groups. It was noted if the cause of death was not treatment related. Mortality in 3 P1 animals (across study groups) were considered not treatment-related; this incidence was low and is not likely to have an impact on results.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were clearly described and appropriate for datasets

Continued on next page . . .

. . . continued from previous page

Study Citation:	NMP Producers Group (1999). Two Generation Reproduction Toxicity Study with N-Methylpyrrolidone (NMP) in Sprague Dawley Rats - Administration in the Diet
Data Type:	2-gen dietary repro tox study in SD rats
HERO ID:	3809436

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 24: Reporting of Data	High	× 2	2	Data for exposure-related findings were presented for all dose groups and endpoints with quantal presentation; summary and individual animal data were reported.
Overall Quality Determination‡		High		1.0	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 30: **Animal toxicity evaluation results of NMP Producers Group 1999 for a 2-generation dietary reproductive toxicity study in Wistar rats**

Study Citation:	NMP Producers Group (1999). Two Generation Reproduction Toxicity Study with N-Methylpyrrolidone (NMP) in Wistar Rats - Administration in the Diet
Data Type:	2-gen dietary repro tox study in Wistar rats
HERO ID:	3809437

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	The test substance was identified as N-methylpyrrolidone (NMP); CAS 872-50-4
	Metric 2:	Test Substance Source	High	× 1	1	The commercial source of the test substance was identified (BASF Aktiengesellschaft). The batch number was reported (Tank 32)
	Metric 3:	Test Substance Purity	High	× 1	1	The purity of the test substance was reported (99.9%); analyzed using gas chromatography
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	An untreated diet control was used
	Metric 5:	Positive Controls	Not Rated	NA	NA	No positive control was used; however, is not necessary for this study type.
	Metric 6:	Randomized Allocation	High	× 1	1	F0 parental rats were randomly allocated into study groups; a computerized randomization program was used according to animal weights 2 days prior to the administration period. F1 parental rats were selected 'by lot'. Selection attempted to "take each litter into account" but if fewer than 25 litters were available for each dose group and gender, additional animals were taken from the available litters. Mating partners were assigned randomly.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	High	× 1	1	The test substance preparation and storage conditions were reported and appropriate for the test substance. Test diets were prepared at intervals that guaranteed the concentration of the test substance in the diet was stable through the feeding period. Homogeneity was analyzed. NMP is reported as stable in the diet for 32 days at room temperature at the tested concentrations. Concentration control analysis was conducted.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Details of exposure administration were reported and appear to be administered consistently across study groups.

Continued on next page . . .

. . . continued from previous page

Study Citation: NMP Producers Group (1999). Two Generation Reproduction Toxicity Study with N-Mythylpyrrolidone (NMP) in Wistar Rats - Administration in the Diet
Data Type: 2-gen dietary repro tox study in Wistar rats
HERO ID: 3809437

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	F0 and F1 administered dietary doses were reported without ambiguity. (0, 50, 160, 500/350 mg/kg bw/day). NMP dietary concentrations for each dose group and sex were adjusted weekly based on body weight and food consumption measurements from the previous week. The measured intakes of NMP correlated well with desired target doses.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Exposure frequency and duration were appropriate for this endpoint; continuously in the diet.
	Metric 11:	Number of Exposure Groups and Dose Spacing	Medium	× 1	2	The number of exposure groups and spacing were justified by the study authors (based on a previously conducted 2-generation reproduction toxicity study). Initially, F0 rats were treated with 0, 50, 160, or 500 mg/kg/day. The high dose level was reduced to 350 mg/kg/day due to excessive pup mortality in F1a pups; thereafter, the administered high dose level was 350 mg/kg/day for the remainder of the study. The dose spacing was appropriate to evaluate the dose-response relationship.
	Metric 12:	Exposure Route and Method	High	× 1	1	The route or method of exposure was reported and suited to the test substance; administered orally via the diet.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	The test animal species, strain, sex, health status, age, and starting body weight were reported. The test animal was obtained Dr. Karl Thomae, Biberach/ Riss, FRG. The test species and strain were an appropriate animal model for the evaluation of the specific outcomes of interest and routinely used for similar study types.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	× 1	1	All husbandry conditions were reported and adequate. Conditions were the same for control and exposed population.
	Metric 15:	Number per Group	High	× 1	1	The number of animals per study group was reported (25 sex/dose in F0 and F1 generations) and appropriate for the study type and outcome analysis.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	The outcome assessment methodologies were appropriate for the endpoints of interest and generally consistent with OECD guidelines for two-generation reproduction testing (OECD TG 416).

Continued on next page . . .

. . . continued from previous page

Study Citation:	NMP Producers Group (1999). Two Generation Reproduction Toxicity Study with N-Mythylpyrrolidone (NMP) in Wistar Rats - Administration in the Diet
Data Type:	2-gen dietary repro tox study in Wistar rats
HERO ID:	3809437

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Details of the outcome assessment protocol were reported and were generally assessed consistently across study groups.
	Metric 18:	Sampling Adequacy	High	× 1	1	Details regarding sampling for the outcomes of interest were reported and the study used adequate sampling for the outcomes of interest
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Not applicable for this study type
	Metric 20:	Negative Control Response	High	× 1	1	The biological responses of the negative control group were reported and were considered adequate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	There were no differences among the study groups in initial body weight. Food consumption was reported; palatability issues were not noted.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	Viability exams and clinical observations were conducted for all study groups. Details regarding health outcomes unrelated to exposure were reported for each study group. There were no differences among groups that could influence the outcome assessment.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were clearly described and appropriate for datasets
	Metric 24:	Reporting of Data	High	× 2	2	Data for exposure-related findings were presented for all dose groups and endpoints with quantal presentation; summary and individual animal data were reported.
Overall Quality Determination‡			High		1.0	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 31: **Animal toxicity evaluation results of E. I. du Pont de Nemours and Company 1990 for Reproductive and developmental inhalation toxicity study in rats on developmental outcomes**

Study Citation:	DuPont (E. I. du Pont de Nemours and Company) (1990). 1-Methyl-2-pyrrolidinone (NMP): Reproductive and developmental toxicity in the rat. Unpublished data, 05 Oct 1990
Data Type:	Reproductive and developmental toxicity study in rats exposed by inhalation (dev)
HERO ID:	3833023

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance identified by name, molecular weight, formula, and boiling point.
	Metric 2:	Test Substance Source	High	× 1	1	Test substance source reported.
	Metric 3:	Test Substance Purity	High	× 1	1	Test substance purity reported (99.867%) along with impurities and their concentrations
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Concurrent sham-treated controls were included.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls not typical for study type.
	Metric 6:	Randomized Allocation	Medium	× 1	2	Animals allocated based on body weight using randomized block design.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Low	× 1	3	Exposure generation and measurement reported in Appendix B. Condensation of test material on chamber walls occurred in exposure group.
	Metric 8:	Consistency of Exposure Administration	Low	× 1	3	Exposures not consistent due to test material condensation in chambers of exposure group; there may have been oral and/or dermal exposure to condensate.
	Metric 9:	Reporting of Doses/Concentrations	Medium	× 2	4	Analytical chamber concentrations were reported in Appendix B. Target concentration not achieved due to condensation in chamber.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Exposure frequency and duration reported and suited to experiment.
	Metric 11:	Number of Exposure Groups and Dose Spacing	Low	× 1	3	Only one exposure level was used for the teratogenicity study (130 ppm) and this exposure level resulted in condensation on chamber walls, with a potential for oral, dermal and inhalation exposure.

Continued on next page . . .

. . . continued from previous page

Study Citation:	DuPont (E. I. du Pont de Nemours and Company) (1990). 1-Methyl-2-pyrrolidinone (NMP): Reproductive and developmental toxicity in the rat. Unpublished data, 05 Oct 1990
Data Type:	Reproductive and developmental toxicity study in rats exposed by inhalation (dev)
HERO ID:	3833023

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Exposure Route and Method	Low	× 1	3	Atmosphere generation was reported; however condensation was observed. The ratio of vapor to aerosol is a function of the relative humidity and temperature. During the first 6 weeks of NMP exposure, the mean daily temperature exceeded 80 degrees Fahrenheit on 29 days. This is expected to significantly impact results.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	Test species, sex, life stage and source were reported and use of the Crl:CD (SD) BR strain was justified. Health status was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	× 1	2	Animal husbandry conditions were reported. Significant variations in temperature was observed in chambers housing control versus treated animals.
	Metric 15:	Number per Group	High	× 1	1	Number per group was reported and appropriate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	Developmental outcome assessment methods were appropriate.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	There was no indication of inconsistency in outcome assessment; outcome assessments were adequately reported.
	Metric 18:	Sampling Adequacy	Medium	× 1	2	Developmental study only included histopathological examinations of one dose group (130 ppm). Condensation of the test material and porphyrin secretion was also observed at this concentration.
	Metric 19:	Blinding of Assessors	Medium	× 1	2	Assessors were not blinded to treatment group for assessment of objective endpoints (narcosis, irritation, performance).
	Metric 20:	Negative Control Response	High	× 1	1	Control response was reported and appropriate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	× 2	6	Variations in temperature and humidity in the test chambers contributed to condensation of the test material. This is expected to influence the outcome.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	× 1	2	Two control dams died due to injury or other reasons; the remaining numbers per group were adequate.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were reported and appropriate; litter served as the unit of statistical analysis.

Continued on next page . . .

. . . continued from previous page

Study Citation:	DuPont (E. I. du Pont de Nemours and Company) (1990). 1-Methyl-2-pyrrolidinone (NMP): Reproductive and developmental toxicity in the rat. Unpublished data, 05 Oct 1990
Data Type:	Reproductive and developmental toxicity study in rats exposed by inhalation (dev)
HERO ID:	3833023

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 24: Reporting of Data	Medium	× 2	4	Litter parameters (e.g., live fetuses/litter) reported as means only without SD or SE.
Overall Quality Determination‡		Medium		1.8	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 32: **Animal toxicity evaluation results of E. I. du Pont de Nemours and Company 1990 for Reproductive and developmental inhalation toxicity study in rats on reproductive outcomes**

Study Citation:	DuPont (E. I. du Pont de Nemours and Company) (1990). 1-Methyl-2-pyrrolidinone (NMP): Reproductive and developmental toxicity in the rat. Unpublished data, 05 Oct 1990					
Data Type:	Reproductive and developmental toxicity study in rats exposed by inhalation (repro)					
HERO ID:	3833023					
Domain		Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance identified by name, molecular weight, formula, and boiling point.
	Metric 2:	Test Substance Source	High	× 1	1	Test substance source reported .
	Metric 3:	Test Substance Purity	High	× 1	1	Test substance purity reported (99.867%) along with impurities and their concentrations
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Concurrent sham-treated controls were included.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls not typical for study type.
	Metric 6:	Randomized Allocation	Medium	× 1	2	Animals allocated based on body weight using randomized block design.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Low	× 1	3	Exposure generation and measurement reported in Appendix B. Condensation of test material on chamber walls occurred in high exposure group.
	Metric 8:	Consistency of Exposure Administration	Low	× 1	3	Exposures not consistent due to test material condensation in high exposure group.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Analytical chamber concentrations were reported in Appendix B.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Exposure frequency and duration reported and suited to experiment.
	Metric 11:	Number of Exposure Groups and Dose Spacing	Medium	× 1	2	3 nonzero exposure concentrations were used; highest exposure level resulted in condensation on chamber walls.
	Metric 12:	Exposure Route and Method	High	× 1	1	Atmosphere generation was reported and appropriate.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	Test species, strain, sex, life stage, and source were reported and justified.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	× 1	1	Animal husbandry conditions were reported and appropriate.
	Metric 15:	Number per Group	High	× 1	1	Number per group was reported and appropriate

Continued on next page . . .

. . . continued from previous page

Study Citation:	DuPont (E. I. du Pont de Nemours and Company) (1990). 1-Methyl-2-pyrrolidinone (NMP): Reproductive and developmental toxicity in the rat. Unpublished data, 05 Oct 1990
Data Type:	Reproductive and developmental toxicity study in rats exposed by inhalation (repro)
HERO ID:	3833023

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	Reproductive outcome assessment methods were reported and appropriate.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	There was no indication of inconsistency in outcome assessment; outcome assessments were adequately reported.
	Metric 18:	Sampling Adequacy	Medium	× 1	2	Histopathology of testes and ovaries was not evaluated except when grossly-observed effects or functional changes occurred.
	Metric 19:	Blinding of Assessors	Medium	× 1	2	Investigators evaluating response to sound in P0 rats were not blinded to exposure status. Other outcomes were not subjective.
	Metric 20:	Negative Control Response	High	× 1	1	Control response reported and appropriate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	× 2	4	Respiratory rate was not reported, but it is not clear that HBCD is an irritant.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	3 dams died due to injury or other reasons; 2 were controls. Remaining numbers per group were adequate.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were reported and appropriate.
	Metric 24:	Reporting of Data	Low	× 2	6	Most data reported as means without SE or SD.
Overall Quality Determination‡			~~High~~ ⟶ Medium§		~~1.5~~	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

§ Evaluator's explanation for rating change: "Confounding by condensation on chamber walls at high exposure level; failure to report measures of variability for most data."

Table 33: **Animal toxicity evaluation results of Ciba-Geigy 1987 for an oral developmental study in mice on growth (early life) and development outcomes**

Study Citation:	Ciba-Geigy Corp (1987). Letter from Ciba-Geigy Corporation to US EPA regarding information on the enclosed reports concerning n-methylpyrrolidone with attachments
Data Type:	Oral developmental mice
HERO ID:	4214093

Domain		Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance identified by name and structure.
	Metric 2:	Test Substance Source	Low	× 1	3	The source was not identified.
	Metric 3:	Test Substance Purity	Low	× 1	3	The purity was not reported; stated to be double distilled.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	Medium	× 2	4	No information on the age/weight of negative (untreated) control animals was provided.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls were not required.
	Metric 6:	Randomized Allocation	Low	× 1	3	Method of randomization not reported.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Low	× 1	3	Information on storage/stability was not provided.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Exposures were administered consistently.
	Metric 9:	Reporting of Doses/Concentrations	Low	× 2	6	Doses were reported as (mm3/kg); however, specific information needed to confirm dose calculations (purity, body weight) was not provided.
	Metric 10:	Exposure Frequency and Duration	Low	× 1	3	Frequency and duration were reported; however, the duration of exposure was inadequate based on OECD 422 standards.
	Metric 11:	Number of Exposure Groups and Dose Spacing	Low	× 1	3	The number of exposure groups and dose spacing were inadequate based on OECD 422 standards.
	Metric 12:	Exposure Route and Method	Low	× 1	3	Translated summaries provided for i.p., oral and inhalation exposures. Limited information provided for generation of inhalation concentrations is.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Low	× 2	6	The source, species, strain, and sex were reported. Age, initial body weight, and health status were not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	× 1	2	Housing, feed, water, temperature, and humidity were reported. Lighting and number of room air changes were not reported.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Ciba-Geigy Corp (1987). Letter from Ciba-Geigy Corporation to US EPA regarding information on the enclosed reports concerning n-methylpyrrolidone with attachments
Data Type:	Oral developmental mice
HERO ID:	4214093

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 15: Number per Group	High	× 1	1	The number of animals was adequate.
Domain 5: Outcome Assessment					
	Metric 16: Outcome Assessment Methodology	Low	× 2	6	Description of outcome assessment methodology is inadequate.
	Metric 17: Consistency of Outcome Assessment	Low	× 1	3	It is difficult to discern whether outcomes were assessed consistently based on translated text.
	Metric 18: Sampling Adequacy	Medium	× 1	2	Sampling was adequate.
	Metric 19: Blinding of Assessors	Not Rated	NA	NA	Blinding not required.
	Metric 20: Negative Control Response	Low	× 1	3	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%)
Domain 6: Confounding / Variable Control					
	Metric 21: Confounding Variables in Test Design and Procedures	High	× 2	2	No confounding variables were reported.
	Metric 22: Health Outcomes Unrelated to Exposure	Low	× 1	3	No information provided regarding health outcomes unrelated to exposure were reported.
Domain 7: Data Presentation and Analysis					
	Metric 23: Statistical Methods	Low	× 1	3	Statistical analysis was not conducted, but data were available to conduct analysis.
	Metric 24: Reporting of Data	Low	× 2	6	Maternal body weights were not reported. Litter data were not presented.
Overall Quality Determination‡		Low		2.4	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 34: **Animal toxicity evaluation results of Ciba-Geigy 1987 for an oral developmental rat study on growth (early life) and development outcomes**

Study Citation:	Ciba-Geigy Corp (1987). Letter from Ciba-Geigy Corporation to US EPA regarding information on the enclosed reports concerning n-methylpyrrolidone with attachments					
Data Type:	Oral developmental rats					
HERO ID:	4214093					
Domain		Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance identified by name and structure.
	Metric 2:	Test Substance Source	Low	× 1	3	The source was not identified.
	Metric 3:	Test Substance Purity	Low	× 1	3	The purity was not reported, but stated to be double distilled.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	Medium	× 2	4	No information on the age/weight of negative (untreated) control animals was provided.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls were not required.
	Metric 6:	Randomized Allocation	Low	× 1	3	Method of randomization not reported.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Medium	× 1	2	Information on storage/stability was not provided, but it is not expected to significantly impact results.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	
	Metric 9:	Reporting of Doses/Concentrations	Medium	× 2	4	Doses were reported as (mm3/kg); however, specific information needed to confirm dose calculations (purity, body weight) was not provided.
	Metric 10:	Exposure Frequency and Duration	Low	× 1	3	Frequency and duration were reported; however, the duration of exposure was inadequate based on OECD 422 standards.
	Metric 11:	Number of Exposure Groups and Dose Spacing	Low	× 1	3	The number of exposure groups and dose spacing were reported and justified, but not considered adequate based on OECD 422 standards.
	Metric 12:	Exposure Route and Method	High	× 1	1	The route and method were appropriate.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Low	× 2	6	The source, species, strain, and sex were reported. Age, initial body weight, and health status were not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	× 1	2	Housing, feed, water, temperature, and humidity were reported. Lighting and air changes were not reported.
	Metric 15:	Number per Group	High	× 1	1	The number of animals was adequate.
Domain 5: Outcome Assessment						

Continued on next page . . .

. . . continued from previous page

Study Citation:	Ciba-Geigy Corp (1987). Letter from Ciba-Geigy Corporation to US EPA regarding information on the enclosed reports concerning n-methylpyrrolidone with attachments
Data Type:	Oral developmental rats
HERO ID:	4214093

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 16:	Outcome Assessment Methodology	Low	× 2	6	Outcome assessment methodology was described; however, it is not adequate based on OECD 422 standards.
	Metric 17:	Consistency of Outcome Assessment	Medium	× 1	2	Outcomes were assessed consistently.
	Metric 18:	Sampling Adequacy	Medium	× 1	2	Sampling was adequate.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding not required.
	Metric 20:	Negative Control Response	Low	× 1	3	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%)
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	No confounding variables were reported.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health outcomes unrelated to exposure were reported.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	Low	× 1	3	Statistical analysis was not conducted, but data were available to conduct analysis.
	Metric 24:	Reporting of Data	Low	× 2	6	Maternal body weights were not reported. Litter data were not presented.
Overall Quality Determination‡			Medium		2.2	
Extracted			No			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 35: **Animal toxicity evaluation results of GAF Chemicals Corp 1991 for developmental toxicity study in rabbits (GD 6-12) on growth (early life) and development outcomes**

Study Citation:	GAF (GAF Chemicals Corp) (1991). Letter from GAF Chem Corp to US EPA submitting preliminary results of n-methyl-2-pyrrolidone developmental toxicity study with attachments
Data Type:	developmental toxicity study in rabbits GD 6-12
HERO ID:	4214113

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Identified by name and CAS number
	Metric 2:	Test Substance Source	Low	× 1	3	Source and/or analytical verification not reported; impact on results uncertain
	Metric 3:	Test Substance Purity	Low	× 1	3	Purity was not reported
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	Medium	× 2	4	Negative control was used, but vehicle was not re-ported
	Metric 5:	Positive Controls	Not Rated	NA	NA	Not applicable for this study type.
	Metric 6:	Randomized Allocation	Low	× 1	3	The study did not report how animals were allocated to study groups
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Unacceptable	× 1	4	Test substance preparation and storage was not re-ported
	Metric 8:	Consistency of Exposure Administration	Unacceptable	× 1	4	Method and vehicle were not reported
	Metric 9:	Reporting of Doses/Concentrations	Medium	× 2	4	Method of administration not reported
	Metric 10:	Exposure Frequency and Duration	Unacceptable	× 1	4	Duration and frequency not reported.
	Metric 11:	Number of Exposure Groups and Dose Spac-ing	Medium	× 1	2	Sufficient number of exposure groups, but doses and spacing were not justified by the study authors; the number of groups and spacing were adequate to show dose-response.
	Metric 12:	Exposure Route and Method	Medium	× 1	2	Method of administration reported.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Low	× 2	6	The source, health status, age and starting body weight of the test animals were not reported
	Metric 14:	Adequacy and Consistency of Animal Hus-bandry Conditions	Low	× 1	3	animal husbandry conditions were not reported
	Metric 15:	Number per Group	Medium	× 1	2	The number of animals in the study was reported and adequate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	Unacceptable	× 2	8	Limited information on outcome assessment re-ported.

Continued on next page . . .

. . . continued from previous page

Study Citation:	GAF (GAF Chemicals Corp) (1991). Letter from GAF Chem Corp to US EPA submitting preliminary results of n-methyl-2-pyrrolidone developmental toxicity study with attachments
Data Type:	developmental toxicity study in rabbits GD 6-12
HERO ID:	4214113

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Consistency of Outcome Assessment	Unacceptable	× 1	4	Details regarding the execution of the study protocol for outcome assessment were not reported.
	Metric 18:	Sampling Adequacy	Low	× 1	3	Details regarding sampling for outcomes of interest were not reported.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Not applicable for this study
	Metric 20:	Negative Control Response	Medium	× 1	2	Control responses reported without measure of variability.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	× 2	6	Initial health status, body weight food/water intake not reported and could impact results.
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	× 1	3	Data on health outcomes unrelated to exposure for each study group was not reported.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	Unacceptable	× 1	4	Statistical analysis not reported, and data required for independent analysis were not reported.
	Metric 24:	Reporting of Data	Low	× 2	6	Statistical analysis not reported, and data required for independent analysis were not reported.
Overall Quality Determination‡			Unacceptable⋆⋆		2.8	
Extracted			No			

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 36: **Animal toxicity evaluation results of Dupont 1979 for developmental range-finding study in rats on growth (early life) and development outcomes**

Study Citation:	Dupont (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
Data Type:	Developmental range-finding: rats
HERO ID:	4214130

Domain		Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	Medium	× 2	4	Test substance identified by name.
	Metric 2:	Test Substance Source	High	× 1	1	The source and lot number were reported.
	Metric 3:	Test Substance Purity	High	× 1	1	Test substance purity was reported
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Concurrent negative controls were included.
	Metric 5:	Positive Controls	High	× 1	1	Concurrent positive controls were used
	Metric 6:	Randomized Allocation	High	× 1	1	Random number assignment sheet was used.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Low	× 1	3	Preparation and storage of test material was not provided. However, it was reported that the positive control agent was prepared fresh daily.
	Metric 8:	Consistency of Exposure Administration	High	× 1	1	Doses were administered consistently.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Duration and frequency were reported.
	Metric 11:	Number of Exposure Groups and Dose Spacing	Medium	× 1	2	The number of groups and dose spacing were reported but not justified.
	Metric 12:	Exposure Route and Method	Medium	× 1	2	The exposure route was appropriate. This was a dermal exposure study. The method of "rubbing it in" was not described with regards to what was used and how it was done and what measures were taken to keep the test substance on.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	High	× 2	2	The source, species, strain, initial body weight, sex, and sexual state were reported. The specific age of the parents was not reported, but they were sexually mature.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	× 1	2	Housing, feed and water were reported. Temperature, humidity, lighting, and air changes were not reported.
	Metric 15:	Number per Group	High	× 1	1	The number of animals was acceptable for a range-finding study.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Dupont (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
Data Type:	Developmental range-finding: rats
HERO ID:	4214130

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	Outcome assessment methodology was appropriate.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding was not required in this study.
	Metric 20:	Negative Control Response	High	× 1	1	Negative control responses were appropriate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	No confounding variables in test design and procedures were noted.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health outcomes unrelated to exposures were reported.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were reported and appropriate.
	Metric 24:	Reporting of Data	High	× 2	2	Data presentation for all outcomes was adequate.
Overall Quality Determination‡			High		1.2	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 37: **Animal toxicity evaluation results of Sitarek et al., 2012 for single generation reproductive toxicity assessment in rats exposed orally study on reproductive outcomes**

Study Citation:	Sitarek, K; Stetkiewicz, J; Wasowicz, 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					
Data Type:	single generation reproductive toxicity assessment in rats exposed orally					
HERO ID:	3043651					
Domain		Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance identified by name and CASRN
	Metric 2:	Test Substance Source	Medium	× 1	2	Test substance obtained from commercial source but without certification or analytical verification of identity.
	Metric 3:	Test Substance Purity	High	× 1	1	Purity reported to be >98%
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	Medium	× 2	4	Negative controls were sham-treated with tap water; however, report did not specify whether water was the vehicle for NMP.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls not typical for this study type.
	Metric 6:	Randomized Allocation	Low	× 1	3	Study did not report how animals were allocated to groups.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Low	× 1	3	Test material prep and storage were not reported.
	Metric 8:	Consistency of Exposure Administration	Medium	× 1	2	Most exposure details were reported, but time of day of gavage administration was not reported. No inconsistencies in exposure administration were reported.
	Metric 9:	Reporting of Doses/Concentrations	Medium	× 2	4	Gavage doses were reported in mg/kg bw; initial body weight was not reported.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Frequency and duration were reported and suited to the study time.
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	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.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Sitarek, K; Stetkiewicz, J; Wasowicz, 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
Data Type:	single generation reproductive toxicity assessment in rats exposed orally
HERO ID:	3043651

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 12:	Exposure Route and Method	Medium	× 1	2	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.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	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.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	× 1	1	All animal husbandry conditions were reported and appropriate.
	Metric 15:	Number per Group	High	× 1	1	22 to 28 females/group tested.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	
	Metric 17:	Consistency of Outcome Assessment	Medium	× 1	2	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).
	Metric 18:	Sampling Adequacy	High	× 1	1	All animals were evaluated for all outcomes.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Subjective outcomes not evaluated.
	Metric 20:	Negative Control Response	High	× 1	1	Negative control responses were reported and adequate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	No potentially confounding factors were noted by the authors or apparent in the study.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	× 1	2	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.
Domain 7: Data Presentation and Analysis						

Continued on next page . . .

. . . continued from previous page

Study Citation:	Sitarek, K; Stetkiewicz, J; Wasowicz, 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
Data Type:	single generation reproductive toxicity assessment in rats exposed orally
HERO ID:	3043651

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 23: Statistical Methods	Medium	× 1	2	Statistical analysis was described and conducted; however, it is not clear that all offspring analyses considered the effect of litter size.
	Metric 24: Reporting of Data	High	× 2	2	
Overall Quality Determination‡		~~High~~ ⟶ Medium§		~~1.6~~	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

§ Evaluator's explanation for rating change: "The only metric that was unacceptable was test substance preparation and storage. The vehicle was not specified in the paper, but controls were given tap water, so water may have been the vehicle. According to the 2001 CICAD, NMP is very stable, and has low volatility from water. Coupled with the fact that the test material was given by gavage, the lack of information on preparation and storage is of limited concern."

Table 38: **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, and thyroid outcomes**

Study Citation:	Sitarek, K; Stetkiewicz, J; Wasowicz, 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
Data Type:	single generation reproductive toxicity assessment in rats exposed orally
HERO ID:	3043651

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	Test substance identified by name and CASRN
	Metric 2:	Test Substance Source	Medium	× 1	2	Test substance obtained from commercial source but without certification or analytical verification of identity.
	Metric 3:	Test Substance Purity	High	× 1	1	Purity reported to be >98%
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	Medium	× 2	4	Negative controls were sham-treated with tap water; however, report did not specify whether water was the vehicle for NMP.
	Metric 5:	Positive Controls	Not Rated	NA	NA	Positive controls not typical for this study type.
	Metric 6:	Randomized Allocation	Low	× 1	3	Study did not report how animals were allocated to groups.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Low	× 1	3	Test material prep and storage were not reported.
	Metric 8:	Consistency of Exposure Administration	Medium	× 1	2	Most exposure details were reported, but time of day of gavage administration was not reported. No inconsistencies in exposure administration were reported.
	Metric 9:	Reporting of Doses/Concentrations	Medium	× 2	4	Gavage doses were reported in mg/kg bw; initial body weight was not reported.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Frequency and duration were reported and suited to the study time.
	Metric 11:	Number of Exposure Groups and Dose Spacing	High	× 1	1	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.
	Metric 12:	Exposure Route and Method	Medium	× 1	2	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.
Domain 4: Test Organism						

Continued on next page . . .

. . . continued from previous page

Study Citation:	Sitarek, K; Stetkiewicz, J; Wasowicz, 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
Data Type:	single generation reproductive toxicity assessment in rats exposed orally
HERO ID:	3043651

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	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.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	× 1	1	All animal husbandry conditions were reported and appropriate.
	Metric 15:	Number per Group	High	× 1	1	22 to 28 females/group tested.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	Low	× 2	6	Endpoints relevant to these outcomes were limited to organ weights, histopathology, and hematocrit.
	Metric 17:	Consistency of Outcome Assessment	Medium	× 1	2	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).
	Metric 18:	Sampling Adequacy	High	× 1	1	All animals were evaluated for all outcomes.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Subjective outcomes not evaluated.
	Metric 20:	Negative Control Response	High	× 1	1	Negative control responses were reported and adequate.
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	No potentially confounding factors were noted by the authors or apparent in the study.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	× 1	2	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.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	Medium	× 1	2	Statistical analysis was described and conducted; however, it is not clear that all offspring analyses considered the effect of litter size.
	Metric 24:	Reporting of Data	Low	× 2	6	Histopathology data were reported qualitatively.
Overall Quality Determination‡			~~Medium~~ ⟶ Low§		~~1.8~~	
Extracted			Yes			

Continued on next page . . .

. . . continued from previous page

Study Citation:	Sitarek, K; Stetkiewicz, J; Wasowicz, 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
Data Type:	single generation reproductive toxicity assessment in rats exposed orally
HERO ID:	3043651

Domain	Metric	Rating†	MWF⋆	Score	Comments††

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

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

where High: ≥ 1 to < 1.7; Medium: ≥ 1.7 to < 2.3; Low: ≥ 2.3 to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.
†† This metric met the criteria for high confidence as expected for this type of study.
§ Evaluator's explanation for rating change: "The only metric that was unacceptable was test substance preparation and storage. The vehicle was not specified in the paper, but controls were given tap water, so water may have been the vehicle. According to the 2001 CICAD, NMP is very stable, and has low volatility from water. Coupled with the fact that the test material was given by gavage, the lack of information on preparation and storage is of limited concern."

Table 39: **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 Citation:	Becci, PJ; Knickerbocker, MJ; Reagan, EL; Parent, RA; Burnette, LW (1982). Teratogenicity study of N-methylpyrrolidone after dermal application to Sprague-Dawley rats Fundamental and Applied Toxicology, 2(2), 73-76
Data Type:	Dermal developmental rats (rf and final-study report in 4214125)
HERO ID:	3539729

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	Medium	× 2	4	Test substance was identified by name.
	Metric 2:	Test Substance Source	Low	× 1	3	The sponsor (GAF Corp) was identified as the source.
	Metric 3:	Test Substance Purity	Low	× 1	3	Concurrent positive controls were used; however, a similar incidence was observed for incomplete ossification between negative and positive controls.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Concurrent negative controls were used in both studies.
	Metric 5:	Positive Controls	Low	× 1	3	Concurrent positive controls were used; however, a similar incidence was observed for incomplete ossification between negative and positive controls.
	Metric 6:	Randomized Allocation	Low	× 1	3	Method of allocation not reported.
Domain 3: Exposure Characterization						
	Metric 7:	Preparation and Storage of Test Substance	Low	× 1	3	Authors note that the positive control solutions were prepared fresh daily, but preparation and storage of the test material was not reported.
	Metric 8:	Consistency of Exposure Administration	Low	× 1	3	Test material was rubbed into skin and the test site remained uncovered. It is unclear whether doses were administered consistently.
	Metric 9:	Reporting of Doses/Concentrations	High	× 2	2	Doses were reported.
	Metric 10:	Exposure Frequency and Duration	High	× 1	1	Frequency and duration were adequate.
	Metric 11:	Number of Exposure Groups and Dose Spacing	Low	× 1	3	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).
	Metric 12:	Exposure Route and Method	High	× 1	1	Route and method were reported.
Domain 4: Test Organism						
	Metric 13:	Test Animal Characteristics	Medium	× 2	4	The source, species, strain, and sex were reported. Age, initial body weight, and health status were not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	× 1	2	Housing, temperature, and lighting were reported. Humidity and air changes were not reported.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Becci, PJ; Knickerbocker, MJ; Reagan, EL; Parent, RA; Burnette, LW (1982). Teratogenicity study of N-methylpyrrolidone after dermal application to Sprague-Dawley rats Fundamental and Applied Toxicology, 2(2), 73-76
Data Type:	Dermal developmental rats (rf and final-study report in 4214125)
HERO ID:	3539729

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Number per Group	High	× 1	1	The number of animals was appropriate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	Medium	× 2	4	Treatment through organogenesis (GD 16 in rats) is recommended for teratology assessments.
	Metric 17:	Consistency of Outcome Assessment	Low	× 1	3	Based on examination of urine, only 1 animal treated at 75 mg/kg showed evidence of exposure.
	Metric 18:	Sampling Adequacy	High	× 1	1	Sampling was adequate.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Blinding was not required.
	Metric 20:	Negative Control Response	Low	× 1	3	A similar incidence was observed for incomplete ossification between negative and positive controls
Domain 6: Confounding / Variable Control						
	Metric 21:	Confounding Variables in Test Design and Procedures	High	× 2	2	No confounding variables were reported.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	× 1	1	No health effects unrelated to exposure were reported.
Domain 7: Data Presentation and Analysis						
	Metric 23:	Statistical Methods	High	× 1	1	Statistical methods were described and appropriate.
	Metric 24:	Reporting of Data	High	× 2	2	Data were reported for all outcomes.
Overall Quality Determination‡			Medium		1.8	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

7 Mechanistic

Table 40: **In vitro evaluation results for Gjoksi et al., 2016 for an inhibition of bromodomain binding study**

Study Citation:	Gjoksi, B.,Ghayor, C.,Bhattacharya, I.,Zenobi-Wong, M.,Weber, F. E. (2016). The bromodomain inhibitor N-methyl pyrrolidone reduced fat accumulation in an ovariectomized rat model Clinical Epigenetics, 8 42
Data Type:	Inhibition of bromodomain binding (AlphaScreen assay)
HERO ID:	3539796

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	The test substance was identified by established nomenclature.
	Metric 2:	Test Substance Source	Low	× 1	3	The source of the test substance was not reported.
	Metric 3:	Test Substance Purity	Low	× 1	3	Purity was not reported.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	Low	× 2	6	Negative control groups were shown in Figure 5. The study indicated that the assay was performed in the absence of the compound (defined as 100% activity). The assay was also performed in the absence if the bromodomain/BET ligand (defined as 0% activity).
	Metric 5:	Positive Controls	Not Rated	NA	NA	The assay test kits may have contained reference compounds, but no data for reference compounds was reported. Reference compound (JQ1) data was provided in an earlier publication by the same authors (Gjoksi et al., 2015; HERO ID 3539797)
	Metric 6:	Assay Procedures	Medium	× 1	2	Methods were partially described and were cited to a standard AphaScreening assay method from BPS Bioscience (San Diego, CA).
	Metric 7:	Standards for Tests	Not Rated	NA	NA	Not applicable to the study type.
Domain 3: Exposure Characterization						
	Metric 8:	Preparation and Storage of Test Substance	Not Rated	NA	NA	Preparation and storage of NMP was not described; however, this information was likely standardized and provided in the AlphaScreen assay instructions (cited to BPS Bioscience, San Diego, CA).
	Metric 9:	Consistency of Exposure Administration	Medium	× 1	2	Exposure details were not reported; however, the AlphaScreen assay is conducted in a microplate format which suggests consistent administration across groups.
	Metric 10:	Reporting of Doses/Concentrations	High	× 2	2	Concentrations were reported in Fig 5.
	Metric 11:	Number of Exposure Groups and Concentration Spacing	Not Rated	NA	NA	Assay duration was not reported; however, this information was likely standardized and provided in the AlphaScreen assay instructions (cited to BPS Bioscience, San Diego, CA).

Continued on next page . . .

. . . continued from previous page

Study Citation:	Gjoksi, B.,Ghayor, C.,Bhattacharya, I.,Zenobi-Wong, M.,Weber, F. E. (2016). The bromodomain inhibitor N-methyl pyrrolidone reduced fat accumulation in an ovariectomized rat model Clinical Epigenetics, 8 42
Data Type:	Inhibition of bromodomain binding (AlphaScreen assay)
HERO ID:	3539796

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Exposure Route and Method	High	× 1	1	9 concentrations were used; spacing across 5 log units.
	Metric 13:	Metabolic Activation	Not Rated	NA	NA	Not applicable to the study design.
Domain 4: Test Model						
	Metric 14:	Test Model	Medium	× 2	4	The test model was reported along with limited descriptive information (recombinant bromodomains and bromodomain ligands or recombinant BET bromodomains and BET ligands).
	Metric 15:	Number per Group	Medium	× 1	2	Number of replicates was not reported; however, error bars in Figure 5 suggest more than one replicate. An earlier publication by the same authors (Gjoksi et al., 2015; HERO ID 3539797) indicated that binding experiments were performed in duplicate.
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	The outcome assessment method reported and was sensitive for the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently across groups (microplate format).
	Metric 18:	Sampling Adequacy	Not Rated	NA	NA	Not applicable to the study design.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Automated measurements only (fluorescence intensity).
Domain 6: Confounding / Variable Control						
	Metric 20:	Confounding Variables in Test Design and Procedures	High	× 2	2	There were no differences reported among study groups (assay test kit).
	Metric 21:	Confounding Variables in Outcomes Unrelated to Exposure	Low	× 1	3	Data on outcome differences unrelated to exposure were not reported (e.g., altered fluorescence by test substance).
Domain 7: Data Presentation and Analysis						
	Metric 22:	Data Analysis	High	× 1	1	Statistical methods and calculation of IC50s were well described and appropriate.
	Metric 23:	Data Interpretation	Not Rated	NA	NA	Scoring and/or evaluation criteria do not apply to the study design.
	Metric 24:	Cytotoxicity Data	Not Rated	NA	NA	A cell-free test system was used.
	Metric 25:	Reporting of Data	High	× 2	2	Data for exposure-related findings were presented for all outcomes by exposure group.
Overall Quality Determination‡			High		1.7	

Continued on next page . . .

. . . continued from previous page

Study Citation:	Gjoksi, B.,Ghayor, C.,Bhattacharya, I.,Zenobi-Wong, M.,Weber, F. E. (2016). The bromodomain inhibitor N-methyl pyrrolidone reduced fat accumulation in an ovariectomized rat model Clinical Epigenetics, 8 42
Data Type:	Inhibition of bromodomain binding (AlphaScreen assay)
HERO ID:	3539796

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 41: **In vitro evaluation results for Gjoksi et al., 2015 for an inhibition of bromodomain binding study**

Study Citation:	Gjoksi, B.,Ghayor, C.,Siegenthaler, B.,Ruangsawasdi, N.,Zenobi-Wong, M.,Weber, F. E. (2015). The epigenetically active small chemical N-methyl pyrrolidone (NMP) prevents estrogen depletion induced osteoporosis Bone, 78 114-121
Data Type:	Inhibition of bromodomain binding (AlphaScreen assay)
HERO ID:	3539797

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	The test substance was identified by established nomenclature.
	Metric 2:	Test Substance Source	Low	× 1	3	The source of the test substance was not reported.
	Metric 3:	Test Substance Purity	Low	× 1	3	Purity was not reported.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	Negative control groups were shown in Figure 1. The study indicated that the assay was performed in the absence of the compound (defined as 100% activity). The assay was also performed in the absence if the bromodomain/BET ligand (defined as 0% activity).
	Metric 5:	Positive Controls	High	× 2	2	The pan-BET inhibitor JQ1 was used as a positive control.
	Metric 6:	Assay Procedures	Medium	× 1	2	Methods were partially described and were cited to a standard AphaScreening assay method from BPS Bioscience (San Diego, CA).
	Metric 7:	Standards for Tests	Not Rated	NA	NA	Not applicable to the study type.
Domain 3: Exposure Characterization						
	Metric 8:	Preparation and Storage of Test Substance	Not Rated	NA	NA	Preparation and storage of NMP was not described; however, this information was likely standardized and provided in the AlphaScreen assay instructions (cited to BPS Bioscience, San Diego, CA).
	Metric 9:	Consistency of Exposure Administration	Medium	× 1	2	Exposure details were not reported; however, the AlphaScreen assay is conducted in a microplate format which suggests consistent administration across groups.
	Metric 10:	Reporting of Doses/Concentrations	High	× 2	2	Concentrations were reported in Figure 1B.
	Metric 11:	Number of Exposure Groups and Concentration Spacing	Not Rated	NA	NA	Assay duration was not reported; however, this information was likely standardized and provided in the AlphaScreen assay instructions (cited to BPS Bioscience, San Diego, CA).
	Metric 12:	Exposure Route and Method	High	× 1	1	9 concentrations were used; spacing across 5 log units.
	Metric 13:	Metabolic Activation	Not Rated	NA	NA	Not applicable to the study design.
Domain 4: Test Model						

Continued on next page . . .

. . . continued from previous page

Study Citation: Gjoksi, B.,Ghayor, C.,Siegenthaler, B.,Ruangsawasdi, N.,Zenobi-Wong, M.,Weber, F. E. (2015). The epigenetically active small chemical N-methyl pyrrolidone (NMP) prevents estrogen depletion induced osteoporosis Bone, 78 114-121
Data Type: Inhibition of bromodomain binding (AlphaScreen assay)
HERO ID: 3539797

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Test Model	Medium	× 2	4	The test model was reported along with limited descriptive information (recombinant bromodomains and bromodomain ligands or recombinant BET bromodomains and BET ligands).
	Metric 15:	Number per Group	High	× 1	1	Binding experiments were performed in duplicate. According to the guide for this assay type, AlphaScreen assays are typified by very low variability between replicate wells. Running samples in duplicate is typically sufficient (the assay can even be run in singlicate).
Domain 5: Outcome Assessment						
	Metric 16:	Outcome Assessment Methodology	High	× 2	2	The outcome assessment method reported and was sensitive for the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	× 1	1	Outcomes were assessed consistently across groups (microplate format).
	Metric 18:	Sampling Adequacy	Not Rated	NA	NA	Not applicable to the study design.
	Metric 19:	Blinding of Assessors	Not Rated	NA	NA	Automated measurements only (fluorescence intensity).
Domain 6: Confounding / Variable Control						
	Metric 20:	Confounding Variables in Test Design and Procedures	High	× 2	2	There were no differences reported among study groups (assay test kit).
	Metric 21:	Confounding Variables in Outcomes Unrelated to Exposure	Low	× 1	3	Data on outcome differences unrelated to exposure were not reported (e.g., altered fluorescence by test substance).
Domain 7: Data Presentation and Analysis						
	Metric 22:	Data Analysis	High	× 1	1	Statistical methods and calculation of IC50s were well described and appropriate.
	Metric 23:	Data Interpretation	Not Rated	NA	NA	Scoring and/or evaluation criteria do not apply to the study design.
	Metric 24:	Cytotoxicity Data	Not Rated	NA	NA	A cell-free test system was used.
	Metric 25:	Reporting of Data	High	× 2	2	Data for exposure-related findings were presented for all outcomes by exposure group.
Overall Quality Determination‡			High		1.4	
Extracted			Yes			

Continued on next page . . .

. . . continued from previous page

Study Citation:	Gjoksi, B.,Ghayor, C.,Siegenthaler, B.,Ruangsawasdi, N.,Zenobi-Wong, M.,Weber, F. E. (2015). The epigenetically active small chemical N-methyl pyrrolidone (NMP) prevents estrogen depletion induced osteoporosis Bone, 78 114-121
Data Type:	Inhibition of bromodomain binding (AlphaScreen assay)
HERO ID:	3539797

Domain	Metric	Rating†	MWF⋆	Score	Comments††

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 42: **In vitro evaluation results for Shortt et al., 2014 for an inhibition of bromodomain binding study**

Study Citation:	Shortt, J., Hsu, A. K., Martin, B. P., Doggett, K., Matthews, G. M., Doyle, M. A., Ellul, J., Jockel, T. E., Andrews, D. M., Hogg, S. J., Reitsma, A., Faulkner, D., Bergsagel, P. L., Chesi, M., Heath, J. K., Denny, W. A., Thompson, P. E., Neeson, P. J., Ritchie, D. S., Mcarthur, G. A., Johnstone, R. W. (2014). The drug vehicle and solvent N-methylpyrrolidone is an immunomodulator and antimyeloma compound 7(4,4), 1009-1019
Data Type:	Inhibition of bromodomain binding (BromoMax screening assay)
HERO ID:	3540731

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Test Substance						
	Metric 1:	Test Substance Identity	High	× 2	2	The test substance was identified by establish nomenclature.
	Metric 2:	Test Substance Source	High	× 1	1	Commercial source was identified.
	Metric 3:	Test Substance Purity	Low	× 1	3	Purity was not reported.
Domain 2: Test Design						
	Metric 4:	Negative and Vehicle Controls	High	× 2	2	IC50 values were reported for DMSO (see Figure 3A). The affinity of NMP for bromodomain proteins was expressed as the percent of control (Table S3).
	Metric 5:	Positive Controls	High	× 2	2	Data were reported for JQ1 (a pan-BET inhibitor).
	Metric 6:	Assay Procedures	Low	× 1	3	Assay procedures were not well described. Bromodomain competition assays were BROMOscan (Discoverex).
	Metric 7:	Standards for Tests	Not Rated	NA	NA	Not applicable to the study type.
Domain 3: Exposure Characterization						
	Metric 8:	Preparation and Storage of Test Substance	Not Rated	NA	NA	Preparation and storage of NMP was not described; however, this information was likely standardized and provided in the Bromoscan assay instructions (cited to Discoverex).
	Metric 9:	Consistency of Exposure Administration	Medium	× 1	2	Exposure details were not reported; however, the BROMOscan assay format suggests consistent administration across groups.
	Metric 10:	Reporting of Doses/Concentrations	High	× 2	2	IC50 was reported (Fig 3A); also 25mM concentration of NMP was reported in Table S3.
	Metric 11:	Number of Exposure Groups and Concentration Spacing	Not Rated	NA	NA	Assay duration was not reported; however, this information was likely standardized and provided in the BROMOoscan assay instructions.
	Metric 12:	Exposure Route and Method	Not Rated	NA	NA	Multiple exposure groups must have been used to generate the IC50 values; however, the concentration were not indicated. The BromoMax screening assay (Table S3) used a single (presumably optimized) concentration of NMP.
	Metric 13:	Metabolic Activation	Not Rated	NA	NA	Not applicable to the study design.

Continued on next page . . .

. . . continued from previous page

Study Citation:	Shortt, J., Hsu, A. K., Martin, B. P., Doggett, K., Matthews, G. M., Doyle, M. A., Ellul, J., Jockel, T. E., Andrews, D. M., Hogg, S. J., Reitsma, A., Faulkner, D., Bergsagel, P. L., Chesi, M., Heath, J. K., Denny, W. A., Thompson, P. E., Neeson, P. J., Ritchie, D. S., Mcarthur, G. A., Johnstone, R. W. (2014). The drug vehicle and solvent N-methylpyrrolidone is an immunomodulator and antimyeloma compound 7(4,4), 1009-1019
Data Type:	Inhibition of bromodomain binding (BromoMax screening assay)
HERO ID:	3540731

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 4: Test Model					
	Metric 14: Test Model	Low	× 2	6	The test model was reported, but no additional details were provided.
	Metric 15: Number per Group	Not Rated	NA	NA	The number of replicates was not indicated, but may have been indicated in the BROMOscan assay instructions.
Domain 5: Outcome Assessment					
	Metric 16: Outcome Assessment Methodology	High	× 2	2	The outcome assessment method reported and was sensitive for the outcome of interest (qPCR).
	Metric 17: Consistency of Outcome Assessment	High	× 1	1	Outcomes were asessed consistently across groups.
	Metric 18: Sampling Adequacy	Not Rated	NA	NA	Not applicable to the study design.
	Metric 19: Blinding of Assessors	Not Rated	NA	NA	Automated measurements only (qPCR).
Domain 6: Confounding / Variable Control					
	Metric 20: Confounding Variables in Test Design and Procedures	High	× 2	2	There were no differences reported among study groups (assay test kit).
	Metric 21: Confounding Variables in Outcomes Unrelated to Exposure	High	× 1	1	Differences among the study replicates or groups in test model unrelated to exposure were not anticipated (qPCR readout).
Domain 7: Data Presentation and Analysis					
	Metric 22: Data Analysis	Low	× 1	3	Statistical analysis was not described.
	Metric 23: Data Interpretation	Not Rated	NA	NA	Scoring and/or evaluation criteria do not apply to the study design.
	Metric 24: Cytotoxicity Data	Not Rated	NA	NA	A cell-free test system was used.
	Metric 25: Reporting of Data	Low	× 2	6	Data for exposure-related findings were not shown for each study group (IC50 values only in Figure 3A).
Overall Quality Determination‡		High		1.7	
Extracted		Yes			

Continued on next page . . .

. . . continued from previous page

Study Citation:	Shortt, J., Hsu, A. K., Martin, B. P., Doggett, K., Matthews, G. M., Doyle, M. A., Ellul, J., Jockel, T. E., Andrews, D. M., Hogg, S. J., Reitsma, A., Faulkner, D., Bergsagel, P. L., Chesi, M., Heath, J. K., Denny, W. A., Thompson, P. E., Neeson, P. J., Ritchie, D. S., Mcarthur, G. A., Johnstone, R. W. (2014). The drug vehicle and solvent N-methylpyrrolidone is an immunomodulator and antimyeloma compound 7(4,4), 1009-1019
Data Type:	Inhibition of bromodomain binding (BromoMax screening assay)
HERO ID:	3540731

Domain	Metric	Rating†	MWF⋆	Score	Comments††

⋆ MWF = Metric Weighting Factor

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

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

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

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

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