Exhibit 5

N-Methylpyrrolidone Producers Group, Inc., Technical Summary in Support of Request for Reconsideration of RFC #23001 (June 12, 2025)

Request for Reconsideration
RFC #23001 (N-Methylpyrrolidone (NMP))
Submitted by B&C® Consortia Management, L.L.C. (BCCM) on behalf of the N-Methylpyrrolidone Producers Group, Inc.

NMP
N-METHYLPYRROLIDONE PRODUCERS GROUP, INC.
2200 PENNSYLVANIA AVENUE, N.W., SUITE 100W, WASHINGTON, D.C. 20037 • (202) 557-3800 • FAX (202) 557-3836
MANAGED BY B&C® CONSORTIA MANAGEMENT, L.L.C.

Exhibit 5
Technical Summary in Support of Request for Reconsideration of RFC #23001
June 12, 2025

B&C® Consortia Management, L.L.C. (BCCM) submits on behalf of the N-Methylpyrrolidone Producers Group, Inc. (NMP Producers Group) this technical summary in support of its Request for Reconsideration (RFR) to appeal the U.S. Environmental Protection Agency's (EPA) denial of its Request for Correction of information (RFC) in the final risk evaluation for n-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP) (RFC #23001).[1,2,3]

EPA has asserted that it responded to RFC #23001 in satisfaction of EPA's Information Quality Guidelines (IQG) when it responded to previous, "overlapping" public comments.[4,5,6] The summary below of EPA's responses to comments by the NMP Producers Group demonstrates that EPA has not met the standards under the Office of Management and Budget (OMB) and EPA's information quality guidelines.

The Group's public comments, as cited in RFC #23001 and the Group's RFR, are available in the dockets for the NMP risk evaluation and EPA's Toxic Substances Control Act

---

1 NMP Producers Group (2023), *Request for Correction of Information on the Toxic Substances Control Act (TSCA) Risk Evaluation for N-Methylpyrrolidone*, N-Methylpyrrolidone Producers Group, Inc., https://www.epa.gov/system/files/documents/2023-05/RFC%2023001%20N-Methylpyrrolidone.pdf.

2 EPA (2023), *Response to Request for Correction of Information on the Toxic Substances Control Act (TSCA) Risk Evaluation for N-Methylpyrrolidone*, U.S. Environmental Protection Agency (EPA), https://www.epa.gov/system/files/documents/2023-08/23001_RFC_NMP-Producers-Group_EPA-Response_eSigned_2023-08-15.pdf ("IQA Guidelines").

3 EPA (2020a), *Risk Evaluation for n-Methylpyrrolidone (2-Pyrrolidone, 1-Methyl-) (NMP) CASRN: 872-50-4*, EPA Document # EPA-740-R1-8009, Office of Chemical Safety and Pollution Prevention (OCSPP), U.S. Environmental Protection Agency (EPA), https://www.epa.gov/sites/default/files/2020-12/documents/1_risk_evaluation_for_n-methylpyrrolidone_nmp_casrn_872-50-4.pdf.

4 OMB, "Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies," 67 Fed. Reg. 8452 (Feb. 22, 2002); EPA, *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity, of Information Disseminated by the Environmental Protection Agency*, EPA/260R-02-008 (October 2002), https://www.epa.gov/sites/default/files/2020-02/documents/epa-info-quality-guidelines_pdf_version.pdf.

5 EPA, *Summary of External Peer Review and Public Comments and Disposition for n-Methylpyrrolidone (NMP)*, EPA Docket No. EPA-HQ-OPPT-2016-0743-0121 at 104-107 (Dec. 2020), https://www.regulations.gov/document/EPA-HQ-OPPT-2016-0743-0121.

6 EPA response to NMP Producers Group (March 9, 2020), EPA Docket No. EPA-HQ-OPPT-2016-0743-0108 (March 2020), https://www.regulations.gov/document/EPA-HQ-OPPT-2016-0743-0108.

(TSCA) Science Advisory Committee on Chemicals (SACC) Review, identified by docket identification (ID) numbers EPA-HQ-OPPT-2016-0743 and EPA-HQ-OPPT-2019-0236 respectively. These comments referenced two key documents:

- The Organisation for Economic Co-operation and Development's (OECD) Screening Information Data Set (SIDS) Initial Assessment Report for NMP, wherein EPA assigned reliability scores based on the scoring system developed by Klimisch *et al*. (1997) and summarized in European Chemicals Agency (ECHA) (2011).[7]

- The February 2021 report by the U.S. National Academies of Sciences, Engineering, and Medicine (NASEM) concluding that EPA's 2018 *Application of Systematic Review in TSCA Risk Evaluations* guidance document (2018 SR Guidance Document) did not meet standards of systematic review methodology, which is required under TSCA Section 26.

In addition, the NMP Producers Group submitted extensive public comments to EPA regarding significant study design flaws identified in Exxon (1991) and EPA's decision to rely on Exxon (1991) as the critical endpoint for chronic toxicity in the final risk NMP evaluation (NMP RE). The public comments explained these concerns and the fact that two subsequent studies (Huntingdon Life Sciences (1999) and BASF Department of Toxicology (1999)) (referenced as NMP Producers Group 1999a, 1999b) did not replicate some of the critical effects observed in Exxon (1991) and were rated as high-quality studies in both the OECD SIDS Assessment and the final NMP RE.

While we recommend that EPA review the Group's original comments in addition to summaries below, we defer to the peer-reviewed assessment submitted in support of RFC #23001 that consisted of a blinded peer-review of the final NMP RE and that assessed Exxon (1991) and NMP Producers Group (1999a and 1999b). The results of this expert panel review were published in a peer-reviewed scientific journal, "Regulatory Toxicology and Pharmacology," titled

[7] OECD (2007), *1-methyl-2-pyrrolidinone, SIDS Initial Assessment Report for SIAM 24, 19-20 April 2007, Paris, France*, Sponsor Country: United States of America, Organisation for Economic Co-operation and Development (OECD), https://hpvchemicals.oecd.org/ui/SponsoredChemicals.aspx (click "Pyrrolidinone, 1-methyl- (CAS 872-50-4), then click on file titled "SIDS_872504.zip"); *Chapter R.4: Evaluation of available information*, Version 1.1, Guidance on Information Requirements and Chemical Safety Assessment, at 1 (PDF at 7), https://echa.europa.eu/documents/10162/17235/information_requirements_r4_en.pdf/d6395ad2-1596-4708-ba86-0136686d205e?t=1323782558175.

"An evaluation of reproductive toxicity studies and data interpretation of N-methylpyrrolidone for risk assessment: An expert panel review," by Kirman, *et al.* (2023).[8]

The panelists concluded that Exxon (1991) is not a high-quality study due to several design flaws that include (1) exceedance of the maximum tolerable dose in the high dose group; (2) failure to adjust feed concentrations of NMP during the lactation period, resulting in NMP doses that were 2- to 3-fold higher than nominal levels; and/or (3) underlying reproductive performance problems in the strain of rats used. Exclusion of Exxon (1991) from the quantitative risk assessment changes the identification of the most sensitive endpoint from male rat fertility to rat fetal/pup body weight. The panel determined that reliance on NMP Producers Group (1999a, 1999b) and the rat fetal/pup body weight endpoint was an appropriate basis for human health risk assessment based on a consideration of the best available science and the weight of the evidence on NMP.

EPA review of the RFC and Kirman *et al*. (2023) would adhere to the OMB Guideline's mandate that presumptive favor is given to peer-reviewed information, which may generally be presumed to be of reasonable objectivity.[9]

Accordingly, we incorporate by reference the substantive arguments raised in the NMP Producers Group's public comments and refer EPA to Kirman, *et al.* (2023). We summarize EPA's responses to public comments on these issues to highlight that EPA has not satisfied requirements under EPA's IQG and must consider RFC #23001.

EPA has not yet responded to RFC #23001 under OMB and EPA information quality guidelines and must review peer-reviewed information submitted in the RFC and issue warranted corrections.

I. Study Quality Ratings and EPA's Systematic Approach under TSCA Section 26

The NMP Producers Group submitted public comments explaining that the international regulatory community had concluded that Exxon (1991) is not a high-quality study

[8] Kirman *et al*. (2023), *An evaluation of reproductive toxicity studies and data interpretation of N-methylpyrrolidone for risk assessment: An expert panel review*, Regul. Toxicol. Pharmacol., Vol. 138, 105337, at 2, https://doi.org/10.1016/j.yrtph.2023.105337.

[9] *Id.* at 8454; 8460.

and included its concerns regarding significant study design flaws that should have had bearing on EPA's assessment under its 2018 systematic review approach to the NMP risk evaluation.

- In 2007, EPA sponsored and presented the SIDS for NMP to the international regulatory community approval at the OECD SIDS Initial Assessment Meeting (SIAM).[10]
  - EPA assigned a Klimisch data reliability score of 2 (*i.e.*, reliable with restrictions) to Exxon (1991).[11]
  - EPA assigned a Klimisch data reliability score of 1 (*i.e.*, reliable without restrictions) to the two subsequent NMP Producers Group's studies, which were unable to reproduce the findings of decreased fertility in the Exxon (1991) study.[12]
- In 2015, EPA's Office of Pollution Prevention and Toxics (OPPT) published the final work plan chemical risk assessment for NMP used in paint strippers and evaluated the studies under OECD's SIDS Initial Assessment Report for NMP.[13] This assessment, therefore, maintained that the Exxon (1991) study was inferior in quality to the two subsequent NMP Producers Group's studies.
  - EPA also concluded that the reproduction and developmental study performed by Sitarek and Stetkiewicz (2008) was "unreliable" due to inconsistencies in the published data.[14]

---

10 OECD (2007), *1-methyl-2-pyrrolidinone, SIDS Initial Assessment Report for SIAM 24, 19-20 April 2007, Paris, France*, Sponsor Country: United States of America, Organisation for Economic Co-operation and Development (OECD).

11 *Id*. at 41.

12 *Id*. at 40. The OECD SIDS Initial Assessment Report references these two studies as NMP Producers Group (1999b) (study involving Wistar rats) and NMP Producers Group (1999c) (study involving Sprague-Dawley rats).

13 EPA (2015), *N-Methylpyrrolidone: Paint Stripper Use, CASRN 872-50-4, TSCA Work Plan Chemical Risk Assessment*, OCSPP, EPA Document # 740-R1-5002, at 48, 52-53, https://www.epa.gov/sites/default/files/2015-11/documents/nmp_ra_3_23_15_final.pdf.

14 *Id*. at 58.

- In the 2020 final NMP RE, EPA explained that it used its 2018 systematic review method (2018 SR Guidance Document) to determine the confidence rating of a data source as high, medium, low, or unacceptable.[15] This defined a data quality rating of "High" as meaning "no notable deficiencies or concerns are identified in the domain metric that are likely to influence results."[16]

  - Applying EPA's 2018 SR Guidance Document in the final NMP RE, EPA assigned a data quality rating of "High" to Exxon (1991).

  - EPA assigned a data quality rating of "High" to Sitarek and Stetkiewicz (2008).

  - EPA assigned NMP Producers Group (1999a) and NMP Producers Group (1999b) data quality ratings of "High" in the final NMP RE.[17]

  - It is unclear how or why EPA concluded that Exxon (1991) and Sitarek and Stetkiewicz (2008) warranted higher data quality and reliability ratings in the Final NMP RE.

  - NASEM reviewed EPA's 2018 SR Guidance Document and issued a consensus study report in 2021 concluding that EPA did not meet the criteria of "comprehensive, workable, objective, and transparent" and that "the OPPT approach to systematic review does not adequately meet the state-of-practice."[18]

  - EPA revised its systematic review method and released the 2021 Draft Protocol, which acknowledged that the 2018 SR Guidance Document "did not have a complete clear and documented TSCA systematic review (SR)

---

15 EPA (2020), *Risk Evaluation for NMP*, at 65.

16 EPA (2018), *Application of Systematic Review in TSCA Risk Evaluations*, OCSPP, EPA Document # 740-P1-8001, at 33, https://www.epa.gov/sites/default/files/2018-06/documents/final_application_of_sr_in_tsca_05-31-18.pdf.

17 EPA (2020), *Risk Evaluation for NMP*, at 227-29; 230; 251-52.

18 NASEM, *The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations*, Consensus Study Report, Highlights, (Feb. 2021) at 4, https://www.nap.edu/resource/25952/TSCA%204-pager%20final.pdf.

Protocol."[19] A systematic review method is required to meet EPA's scientific standards under TSCA Section 26.

- EPA's Responses to Public Comments:

  - In its responses to comments, EPA asserted that study quality ratings from other organizations lack transparency and may not be informative.[20] EPA would rely instead on its own analysis designating Exxon (1991) as a "high-quality" study under its 2018 SR Document.

  - In response to comments that the 2018 SR Document did not adhere to the standards of TSCA Section 26 following NASEM review and EPA's issuance of the 2021 Draft Systematic Review protocol, EPA issued a conclusory statement that the final NMP RE meets TSCA Section 26 standards and that EPA will not cause delays by retroactively applying an amended approach to the final NMP RE.[21]

- RFC #23001 and RFR:

  - EPA has not addressed its decision in the final NMP RE to rate Exxon (1991) and Sitarek and Stetkiewicz (2008) as high-quality studies under OMB and EPA information quality guidelines. We maintain that EPA's decision lacks transparency and was erroneous.

  - Apart from its cursory statement, EPA does not explain why study quality ratings "from other organizations" are unreliable. The organization in

---

19 EPA, *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances Version 1.0, A Generic TSCA Systematic Review Protocol with Chemical-Specific Methodologies* (2021 Draft Protocol), OCSPP, EPA Document # EPA-D-20-031 (Dec. 2021) at 25, https://www.epa.gov/system/files/documents/2021-12/draft-systematic-review-protocol-supporting-tsca-risk-evaluations-for-chemical-substances_0.pdf.

20 EPA, "Summary of External Peer Review and Public Comments and Disposition for n-Methylpyrrolidone (NMP)," at 105.

21 EPA, "n-Methylpyrrolidone (NMP); Revision to Toxic Substances Control Act (TSCA) Risk Determination: Response to Public Comments," EPA Docket No. EPA–HQ–OPPT–2016–0743 (December 2022), at 2-3, https://www.epa.gov/system/files/documents/2022-12/NMP%20RD%20RtC_12-12-22.pdf.

question is OECD, which develops international standards for the testing of chemicals.

- EPA does not explain why OECD's study quality ratings "lack transparency" or "may not be informative."

- The inexplicability of this assertion is amplified by the fact that EPA's IQG directly cites to OECD SIDS protocol. As cited in the IQG, EPA's "Guidelines for Reproductive Toxicity Risk Assessment" explicitly refers to OECD's SIDS protocol for reproductive toxicity screening tests.[22]

- The 2018 SR Guidance Document used in the Final NMP RE does not meet the standards of TSCA Section 26. This demonstrates further significant issues with EPA's departure from international consensus in the final NMP RE and its reliance on Exxon (1991). EPA's stated concerns regarding the potential for delay do not invalidate EPA's requirement to comply with TSCA Section 26 or OMB and EPA information quality guidelines.

- The international consensus on study quality and results is indisputable. The 1991 Exxon study cannot be considered a high-quality study and should not be the basis for EPA's human health assessment.

EPA has inexplicably depreciated the significance of international OECD study quality ratings while relying on its own study quality rating criteria that it has already acknowledged as insufficient. EPA has not addressed this issue following the 2021 determination that EPA's 2018 SR Guidance Document did not meet the standards of TSCA Section 26. This warrants correction.

II. Study Design Flaws Indicate that Exxon (1991) Is Not a High-Quality Study

In addition to addressing EPA's divergence from OECD's 2007 SIDS Initial Assessment Report for NMP, the NMP Producers Group submitted public comments raising serious concerns with study design for Exxon (1991) indicating that EPA should not assess the study as "high-quality" in the NMP RE. As explained above, Kirman *et al.* (2023) included a peer-

[22] "Guidelines for Reproductive Toxicity Risk Assessment," 61 Fed. Reg. 56274, 56281 (Oct. 31, 1996), https://www.govinfo.gov/content/pkg/FR-1996-10-31/pdf/96-27473.pdf.

reviewed assessment of EPA's final NMP RE and addressed EPA's assessment of Exxon (1991) and the two NMP Producers Group studies (NMP Producers Group 1999a, 1999b).

- **EPA's Response to Comments:** EPA acknowledged but dismissed the study quality issues raised by the NMP Producers Group and EPA's TSCA SACC without either a robust explanation or any explanation.

  - EPA began its response by stating: "Study quality issues raised in public comments for the most part reflect choices in study design (*e.g.*, not adjusting the concentration of NMP in the feed), non-critical reporting issues, and speculation about the adequacy of the study animals."[23]

  - EPA then states that concerns regarding decreased fertility in some Charles River rats was due solely to the assumption that the Exxon (1991) study rats might be carriers of genetically-mediated testicular abnormalities leading to decreased fertility. EPA states that it traced the source of the Exxon study animals and did not find evidence that the study animals were carriers of this genetic variant. Therefore, because the issue was "merely speculative," EPA rejected these concerns.[24]

  - EPA did not address comments on the study design regarding the increased probability of brother:sister matings under the mating schematic of Exxon (1991). The increased probability of inbreeding means that the animals were more likely to experience reproductive failure. These concerns, therefore, were not limited to potential genetic abnormalities, but concerned the male and female rats used in the study. EPA has not addressed this issue.

  - EPA did not address concerns about the issues with the failure of laboratory staff to detect the mating of some animals. It is not clear whether this is the "non-critical reporting issue" described by EPA in its response to comments, and if so, why EPA believes this issue is "non-critical." EPA has not addressed this issue.

[23] EPA, "Summary of External Peer Review and Public Comments and Disposition for n-Methylpyrrolidone (NMP)," at 105.

[24] *Id.* at 106.

- EPA did not address the concerns regarding the underestimation of the NMP dose based on the failure in Exxon (1991) to adjust the concentrations of NMP in feed. As explained in the Group's comments, the impacts of this design flaw impacted the reproducibility of Exxon (1991). When the feed levels were appropriately adjusted for changes in food consumption (NMP Producers Group 1999a, 1999b), the effects on fertility and fecundity were not observed in rats exposed to the same dose range. EPA has not addressed this issue.

- RFC #23001 and RFR:

  - The peer-reviewed analysis in Kirman *et al.* (2023) submitted with RFC #23001 includes an analysis of the study design flaws in Exxon (1991) that demonstrate that it is not a high-quality study. We refer EPA to this 12-page article that outlines significant information quality concerns under OMB and EPA's information quality guidelines.

  - For the purposes of this RFR, we note that EPA did not give weight in its response to public comments to significant study design flaws that had bearing on the reliability and reproducibility of information EPA relied upon in the final NMP RE. EPA's response to public comments on study design issues did not adhere to EPA's IQG and do not form a basis for EPA to reject evidence submitted in RFC #23001 and the results of the peer-review in Kirman *et al.* (2023).

III. Reproducibility of Influential Scientific Information

- **NMP Producers Group's Public Comments:** It is inappropriate for EPA to continue its reliance on effects from a two-generation reproduction toxicity study in rats (Exxon 1991) that were not reproducible in two subsequent two-generation reproduction toxicity studies in rats (*i.e.*, NMP Producers Group 1999a, 1999b).

  - Based on Exxon (1991), EPA concluded that reductions in male fertility and female fecundity indices observed in an earlier two-generation reproductive toxicity study with Sprague-Dawley rats (Exxon 1991) were biologically (although not statistically) significant at the low and intermediate oral doses (50 and 160 mg/kg body weight (bw)/day) and that a no observed adverse effect level (NOAEL) was not achieved. To clarify the Exxon 1991 study findings, the NMP Producers Group independently repeated the study at the

same doses at two different facilities using two strains of rats (Sprague-Dawley at Huntingdon and Wistar at BASF). In both strains, NMP had no adverse effects on the reproductive performance or fertility of the F0 or F1 parental animals in all dose groups.

- Accordingly, EPA's position that the fertility/fecundity effects in the Exxon study are purportedly "biologically significant" is not supported by the two additional two-generation reproductive toxicity studies sponsored by the NMP Producers Group, which had higher quality ranking scores, nor is it supported by the other studies cited by EPA as providing such support (Sitarek *et al.* 2012 and Sitarek and Stetkiewicz 2008).

- **EPA's Response to Comments:** EPA *did not* address the issue that the effects in the Exxon (1991) study were not replicated in two subsequent studies.

  - In the final RE, EPA acknowledges that the subsequent two NMP Producers Group studies did not replicate effects on reduced fertility in Exxon (1991) but does not provide any further analysis, except to state that evidence of reproductive toxicity is "inconsistent across studies."[25]

  - In response to SACC comments regarding the difference in outcomes, which also stated that EPA should "consider using greater weights for data collected from the more applicable exposure pathways and accompany the quality review score of a study with the associated weights for data on health outcomes addressed in that study," EPA reasserted its decision to rely on Exxon (1991) without fully considering SACC's comments.[26]

    - EPA stated that "differences in outcomes across studies may be due to differences in study design (exposure timing and duration, timing of outcome evaluation, *etc*), or other unknown confounding biological factors (strain sensitivity, metabolic changes, *etc*). While statistical power is a relevant consideration, these biological aspects of study design that

[25] EPA (2020), *Risk Evaluation for NMP*, at 226.

[26] *Id.* at 107-108.

could influence outcome are also important contributors to study outcomes."[27]

- **RFC #23001 and RFR:** The peer-reviewed evaluation in RFC #23001 and Kirman *et al.* (2023) addressed EPA's reliance on NMP-related effects on male fertility and female fecundity in Exxon (1991) that were not observed in subsequent, higher quality studies (NMP Producers Group 1999a, 1999b).

  - For the purposes of this RFR, we confirm that to date, EPA has failed to respond to or address the fact two subsequent studies could not replicate the effects of Exxon (1991) and that this finding falls short of OMB and EPA's reproducibility standard. The fact that subsequent studies could not replicate the effects of Exxon (1991) is not an "inconsistency," as EPA described, but a significant flaw in EPA's Final NMP RE and EPA's response to the RFC.

  - EPA acknowledged in its response to comments that differences in study design may result in the differences in outcomes, but as noted above, refused to consider that significant flaws in the study design for Exxon (1991) is critical in study design rating and the reliability of the study.

  - Kirman *et al.* (2023) explains that Exxon (1991) and the two NMP Producers Groups studies (NMP Producers Group 1999a, 1999b) followed the same basic study design but that the key differences in Exxon (1991) were the result of design *flaws*. The NMP Producers Group's studies replicated and improved the study design in Exxon (1991) by eliminating design flaws, which resulted in differing outcomes.

  - EPA's IQG specifies that EPA will ensure reproducibility for disseminated original and supporting data.[28] The "reproducibility standard" under OMB Guidelines for influential information is intended to increase the credibility of federal decisions and is a higher standard that requires heightened transparency. In relying in its risk evaluation on information that is not "capable of being substantially reproduced," EPA has not met the

[27] *Id.* at 107.

[28] EPA, Information Quality Guidelines, at Section A.3.5 (Reproducibility).

reproducibility or transparency standards mandated under OMB Guidelines.[29]

- Regarding reproducibility, EPA's "Guidelines for Reproductive Toxicity Risk Assessment" state the following:

> The judgment of whether data are sufficient or insufficient should consider a variety of parameters that contribute to the overall quality of the data, such as the power of the studies (e.g., sample size and variation in the data), the number and types of endpoints examined, *replication of effects*, relevance of route and timing of exposure for both human and experimental animal studies, and the appropriateness of the test species and dose selection in experimental animal studies.[30]

> Although a single study of high quality could be sufficient to achieve a relatively high level of confidence, *replication increases the confidence that may be placed in such results*.[31]

There is ample evidence showing that EPA's characterization of Exxon (1991) as a "high-quality" study was demonstrably false; EPA cannot continue to rely on Exxon (1991) under OMB and EPA Guidelines as it does not satisfy the standards for reproducibility and transparency. This is further supported by RFC #23001 and Kirman *et al.* (2023) and requires correction of the final NMP RE.

IV. Chronic Toxicity Endpoint Selection

- **NMP Producers Group's Public Comments**: For its chronic toxicity assessment, EPA relied upon the reproductive toxicity study of Exxon (1991) and adopted a different endpoint (reduced fertility/fecundity) than was used in the 2015 TSCA assessment for NMP (fetal body weight changes). Having presented the NMP data set to the international regulatory community for approval at the OECD SIAM in 2007, EPA was aware that the critical chronic effect seen in the referenced study as well as others is a decrement in fetal/pup body weight. EPA's assessment relies on the results from a single reproductive

[29] 67 Fed. Reg. at 8460.

[30] 61 Fed. Reg. at 56303-56304. Emphasis added.

[31] *Id.* at 56304. Emphasis added.

toxicity study (Exxon 1991) for establishing point of departure (POD). Multiple follow-up reproductive studies have been conducted for NMP (Thornton, 1999; Hellwig and Hildebrand, 1999; Solomon *et al.*, 1995), providing a weight-of-evidence that counters the results of Exxon (1991).

- **EPA's Response to Comments**: EPA stated that it selected a chronic POD by relying solely on available studies and stating "there is no way to determine which periods of exposure contributed the most" to the reduced male fertility and female fecundity in rats following exposures throughout gestation, lactation, development, and prior to mating.[32]

  - In response to SACC comments that it appeared EPA was selecting the most sensitive toxic endpoint, rather than relying on the best available science, EPA asserted its claim that "EPA considered the reduced fertility reported in several studies to be a robust, biologically plausible endpoint that is highly relevant to humans and that is consistent with the continuum of reproductive and developmental endpoints reported across available studies."[33] The studies that EPA relies on in support of this assertion are Exxon (1991), Sitarek *et al.* (2012), and Sitarek and Stetkiewicz (2008).[34]

  - Regarding the statement that the NMP Producers Group studies "more accurately represent the true sensitivity of rats to NMP-related effects on fertility/fecundity," EPA listed the following points:

    - Concurrent controls were used for statistical comparison to the treated groups in the Exxon 1991 study, not controls from the NMP Producers studies, and the P and F1 control males did not exhibit these effects.

    - It is possible that the fertility response in the Exxon (1991) study is more representative of the human population, and thus a better predictor of the potential effects of NMP for human health risk assessment. Infertility has been reported to affect approximately 15% of couples globally; males are

[32] EPA, "Summary of External Peer Review and Public Comments and Disposition for n-Methylpyrrolidone (NMP)," at 107.

[33] *Id.* at 107-108.

[34] *Id.* at 109.

solely responsible for 20-30% of infertility cases and contribute to 50% of cases overall (Agarwal *et al.*, 2015; doi:10.1186/s12958-015-0032-1). In the United States, 9% of men aged 25-44 years of age reported consulting a physician on infertility issues during their lifetime. In support of this assertion, EPA cited to a CDC webpage that is no longer available ("https://www.cdc.gov/reproductivehealth/infertility/").

- The weight of the scientific evidence for male reproductive toxicity in the risk evaluation (Section 3.2.4.2.) includes all reasonably available data that inform the issue (Sitarek and Stetkiewicz, 2008; NMP Producers Group, 1999a, b; Exxon Biomedical, 1991) and studies that provide information and support for the mechanistic plausibility of male reproductive toxicity following NMP exposures.

- EPA speculates about a mechanism that could connect NMP exposure to decreased fertility, but acknowledges that "At this time, there is no direct evidence for the effect of NMP-mediated inhibition of this testis-specific bromodomain protein…"

■ **RFC #23001 and RFR:** We again refer EPA to the peer-reviewed analysis in Kirman *et al.* (2023) submitted with RFC #23001. This demonstrates that EPA cannot rely on Exxon (1991) to establish male fertility as the basis for its quantitative human health risk assessment and that the weight of the evidence for reproductive toxicity supports fetal/pup body weight as the most sensitive endpoint. To address further EPA's assertion that it addressed concerns with Exxon (1991) in its response to comments, we note below serious concerns regarding EPA's explanations.

➢ EPA has no data to support that global populations are exposed to NMP, much less that all are exposed at a dose that would affect fertility. It is more plausible to suggest that increased surface temperature from climate change increases testicular temperature which is a well-known cause of decreased fertility.

➢ Here, EPA bootstraps multiple weaker studies without considering the lack of effects on fertility in multiple stronger, higher quality studies.

- EPA asserts that it considered all reasonably available data under the weight of the evidence in the final NMP RE, including NMP Producers Group (1999a, 1999b); but if this were the case, EPA's decision to continue to rely on Exxon (1991) is even more inexplicable. EPA's decision not to shift its reliance on Exxon (1991) in the draft NMP RE to the later two-generation studies in the final NMP RE rings hollow. As EPA's decision is not supported by the weight of the scientific evidence, it appears it was based instead on perceived time and resource constraints.

    - In its consideration of RFC #23001, EPA speculates internally that the RFC is a tactic to delay issuance of the risk management rule when EPA itself delayed proposing the risk management rule so that it could reconsider the previous risk determination. EPA could have reviewed the RFC and either responded robustly or updated its risk evaluation prior to publishing the updated risk determination. It simply chose not to.

V. Additional Concerns

EPA's response to public comments did not reference or indicate that EPA investigated its compliance with standards required under the OMB and EPA IQGs. EPA furthermore did not explain the procedures under EPA's IQG, which includes the right to appeal EPA's response to a request for correction of information.

In addition to the above and the peer-reviewed analysis provided in Kirman *et al.* (2023), RFC #23001 included a reevaluation of chronic occupational exposure scenarios for workers and occupational non-users (ONU).[35] EPA has yet to address these issues under OMB and EPA IQGs.

---

[35] EPA (2020d), *Supplemental Information File on Occupational Risk Calculations, Final Risk Evaluation for n-Methylpyrrolidone, CASRN: 872-50-4*, Microsoft Excel file name: 16._nmp_supplemental_information_file_on_occupational_risk_calculations_0.xlsx, https://www.epa.gov/sites/default/files/2020-12/16._nmp_supplemental_information_file_on_occupational_risk_calculations_0.xlsx.

VI. Conclusion

OMB and EPA information quality guidelines emphasize the need for reproducibility and transparency, among other standards, and establish the presumption of favoring information subject to formal, independent, external peer-review. The guidelines further ensure a process for objective review, with an opportunity for stakeholders to appeal an agency decision.

The NMP Producers Group's RFC adhered to these requirements and submitted peer-reviewed evidence demonstrating that EPA's final NMP RE did not adhere to the requirements of reproducibility or transparency. EPA relies inexplicably on information that is not reproducible in a risk evaluation that is itself not reproducible: The outcome of EPA's assessment in 2020 using its 2018 SR Guidance Document would not be reproduced by EPA in 2025 when applying a systematic review protocol that meets the standards of TSCA Section 26.

Moreover, EPA's responses to public comments did not meet the requirements under OMB and EPA IQGs: EPA did not address or consider the guidelines in issuing its response, evaluating public comments, notify stakeholders of the opportunity to appeal, or respond substantively to significant concerns raised. Just as the RFC process should not be used to delay the risk management rule, neither should the fact that correcting the risk evaluation would delay the rule be used to justify using science that does not meet the statutory language.

Accordingly, the NMP Producers Group's RFR demonstrates the need for substantive review and correction.