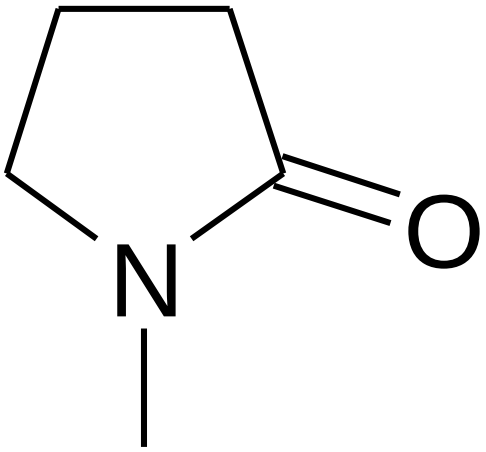
United States
Environmental Protection Agency

Office of Chemical Safety and Pollution Prevention
December 2020

Summary of External Peer Review and Public Comments and Disposition for n-Methylpyrrolidone (NMP)

Response to Support Risk Evaluation of n-Methylpyrrolidone (NMP)



December 2020

Table of Contents

This document summarizes the public and external peer review comments that EPA's Office of Pollution Prevention and Toxics (OPPT) received for the risk evaluation of *n*-methylpyrrolidone (NMP). It also provides EPA's response to the comments received from the public and the peer review panel.

EPA appreciates the valuable input provided by the public and peer review panel. The input resulted in numerous revisions to the hazard summary.

Peer review charge questions[1] are used to categorize the peer review and public comments into specific issues related to the main themes.

1. Environmental Exposure Assessment, Including Environmental Fate and Transport and Environmental Release Assessment
2. Ecological Exposure, Hazard Assessment, and Risk Characterization
3. Occupational and Consumer Exposure Assessment
4. Human Health Hazard
5. Human Health Dose-response Assessment
6. Risk Characterization
7. Content, Organization and Clarity of the Document

All peer review comments for the seven charge questions are presented first, organized by charge question in the following section. These are followed by the public comments. For each theme, general comments pertaining to all chemicals are presented first, and then additional comments pertaining to only one or several chemicals follows.

[1] These are the questions that EPA submitted to the panel to guide the peer review process.

1. List of Comments

#	Docket File	Submitter
31	EPA-HQ-OPPT-2019-0236-0031	David Isaacs, Semiconductor Industry Association (SIA)
32	EPA-HQ-OPPT-2019-0236-0032	Suzanne Hartigan, Senior Director, Regulatory and Technical Affairs, American Chemistry Council (ACC)
33	EPA-HQ-OPPT-2019-0236-0033	Kathleen M. Roberts, NMP Producers Group, Inc.
34	EPA-HQ-OPPT-2019-0236-0034	Jonathan Kalmuss-Katz, Staff Attorney, Earthjustice (12-04-2019)
37	EPA-HQ-OPPT-2019-0236-0037	Sharon Shindel, Corporate Industrial Hygienist, Intel Corporation
38	EPA-HQ-OPPT-2019-0236-0038	Jennifer Sass, Senior Scientist, Natural Resources Defense Council (NRDC)
39	EPA-HQ-OPPT-2019-0236-0039	Weihsueh A. Chiu, Professor, Veterinary Integrative Biosciences, Texas A&M University
40	EPA-HQ-OPPT-2019-0236-0040	Veena Singla, Associate Director, Program on Reproductive Health and the Environment, School of Medicine, University of California, San Francisco
42	EPA-HQ-OPPT-2019-0236-0042	Eric Berg, Deputy Chief, California Division of Occupational Safety and Health (Cal/OSHA)
44	EPA-HQ-OPPT-2019-0236-0044	Anonymous
45	EPA-HQ-OPPT-2019-0236-0045	Sheryl Beauvais, Senior Compliance Analyst, Hach Company
46	EPA-HQ-OPPT-2019-0236-0046	Attorneys General of New York, Illinois, Maine, Maryland, Massachusetts, Minnesota, New Jersey, Oregon, Vermont, and Washington
47	EPA-HQ-OPPT-2019-0236-0047	Mark Kohorst, Director, Environment Health & Safety, National Electrical Manufacturers Association (NEMA)
48	EPA-HQ-OPPT-2019-0236-0048	Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, University of California, San Francisco
49	EPA-HQ-OPPT-2019-0236-0049	Aaron Rice, Environmental Health & Safety Director, EaglePicher Technologies, LLC
50	EPA-HQ-OPPT-2019-0236-0050	Janet M. Carlock, EHS Regulatory Manager, FUJIFILM Holdings America Corporation
51	EPA-HQ-OPPT-2019-0236-0051	Safer Chemicals Healthy Families, Environmental Health Strategy Center, Natural Resources Defense Council, and Earthjustice
52	EPA-HQ-OPPT-2019-0236-0052	David Isaacs, SIA

53	EPA-HQ-OPPT-2019-0236-0053	Riaz Zaman, Counsel, Government Affairs, American Coatings Association (ACA)
54	EPA-HQ-OPPT-2019-0236-0054	Suzanne Hartigan, Senior Director, Regulatory and Technical Affairs, ACC
55	EPA-HQ-OPPT-2019-0236-0055	Dianne C. Barton, Chair, National Tribal Toxics Council (NTTC)
56	EPA-HQ-OPPT-2019-0236-0056	Martha Marrapese, Wiley Rein LLP on behalf of the Lithium Cell Manufacturers' Coalition
57	EPA-HQ-OPPT-2019-0236-0057	Kathleen M. Roberts, Manager, NMP Producers Group
58	EPA-HQ-OPPT-2019-0236-0058	Kathleen M. Roberts, Manager, NMP Producers Group (Attachments)
59	EPA-HQ-OPPT-2019-0236-0059	Richard A. Denison, Lead Senior Scientist, Environmental Defense Fund (EDF)
60	EPA-HQ-OPPT-2019-0236-0060	Hesham M. Soliman, Senior Product Steward, Global Chemical Control, Lyondell Chemical Company
61	EPA-HQ-OPPT-2019-0236-0061	Earthjustice and the Occupational Safety & Health Law Project on behalf of the American Federation of Labor and Congress of Industrial Organizations (AFL-CIO); International Union, United Automobile, Aerospace, and Agricultural Implement Workers of America (UAW); North America's Building Trades Unions (NABTU); and United Steel, Paper and Forestry, Rubber, Manufacturing, Energy, Allied Industrial and Service Workers International Union (United Steelworkers)
62	EPA-HQ-OPPT-2019-0236-0062	Earthjustice and the Occupational Safety & Health Law Project on behalf of the American Federation of Labor and Congress of Industrial Organizations (AFL-CIO); International Union, United Automobile, Aerospace, and Agricultural Implement Workers of America (UAW); North America's Building Trades Unions (NABTU); and United Steel, Paper and Forestry, Rubber, Manufacturing, Energy, Allied Industrial and Service Workers International Union (United Steelworkers) (Exhibits)
63	EPA-HQ-OPPT-2019-0236-0063	Lawrence E. Culleen, Arnold & Porter on behalf of Chemical Users Coalition (CUC)
64	EPA-HQ-OPPT-2019-0236-0064	John Currier, Corporate EHS TSCA Program Manager, Intel Corporation

2. Environmental Fate and Exposure

Environmental Fate and Exposure		
Charge Question 1.1: Please comment on the data, approaches and/or methods used to characterize exposure to aquatic receptors.		
#	**Summary of Comments for Specific Issues Related to Charge Question 1**	**EPA Response**
Scope of fate and exposure assessment – Other regulatory programs		
SACC	**SACC COMMENTS:** • Recommendation: Provide a summary of the focus, status, and results of NMP assessments completed or progressing under other EPA regulatory programs. • The evaluation must clearly state which environmental releases are covered by other regulations and are not associated with TSCA.	EPA provides a summary of assessments that have been previously completed for NMP in Table 1-5 and a summary of the regulatory history of NMP in Appendix A. EPA has added Section 1.4.2, which describes exposure pathways and risks that fall under the jurisdiction of other EPA administered statutes or regulatory programs. As described in Section 1.4.2, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA believes that coordinated action on exposure pathways and risks addressed by other EPA-administered statutes and regulatory programs is consistent with statutory text and legislative history, particularly as they pertain to TSCA's function as a "gap-filling" statute, and also furthers EPA aims to efficiently use Agency resources, avoid duplicating efforts taken pursuant to other Agency programs, and meet the statutory deadline for completing risk evaluations. EPA has therefore tailored the scope of the risk evaluation for NMP using authorities in TSCA Sections 6(b) and 9(b)(1). Pathways that are within the scope of the risk evaluation are described in Section 1.4.3.
Scope of fate and exposure assessment- Exposures/receptors not assessed		
SACC	**SACC COMMENTS:** • Recommendation: Determine potential NMP exposures to threatened and endangered species and to honeybees.	The TSCA risk evaluation focuses on exposures for environmental receptors associated with conditions of use for the NMP. The assessment focuses on environmental receptors that may be exposed to NMP as a result of the conditions of use and associated

	• NMP has demonstrated toxicity to honeybees (Fine and Mullin, 2017). • No assessment of exposures to threatened or endangered species is provided in the draft risk evaluation. EFAST has a feature that allows "searching for endangered species in the vicinity of specific facilities."	hazards to those affected species.
SACC	**SACC COMMENTS:** • Recommendation: Discuss the evidence for uptake of NMP by terrestrial plants and the potential for trophic transfer to herbivores. • There is evidence that terrestrial plants take up NMP (Doucette et al., 2018; Dettenmaier et al., 2009), and hence uptake and exposure to terrestrial plants should be assessed, particularly as part of a bioconcentration process (NMP Risk Evaluation, p. 48). Such uptake would provide a route for trophic transfer of NMP to herbivores. Additional data are needed to better understand these risks and to determine if plant uptake poses unreasonable risks to herbivores.	During problem formulation, EPA identified several pathways (including sediment, ambient water, land-applied biosolids, and ambient air) that did not require further analysis because environmental fate properties and first-tier analysis of environmental release data indicated that exposures were well below levels of concern. Terrestrial environmental receptors were therefore not further evaluated. EPA's conclusions about risks from exposure through ambient air, ambient water, sediment, and land-applied biosolids are summarized in the Problem Formulation and in Section 4.6.2.3 of the risk evaluation.
Include a mass balance analysis		
SACC	**SACC COMMENTS:** • Recommendation: Provide an analysis matching annual imports and manufactured NMP amounts to NMP releases and amounts used in products/processes (a mass balance analysis), incorporate analysis findings into the life cycle diagram, and discuss how these findings impact the estimated water releases used in this draft risk evaluation.. • The life cycle discussion should be expanded to paint a more complete picture on sources of NMP	EPA developed an approach and conducted a mass balance analysis for NMP. The analysis, which accounted for 83% of the NMP production volume, is summarized in Section 1.4.1 and details are provided in Appendix C.

	emissions, distribution, and sinks useful for providing a mass balance analysis for all NMP produced and imported. Additional information about NMP could be added to Fig. 1-1 to increase utility and transparency (*e.g.*, some uses are missing, as noted above; the disposal box is uninformative).	
Clarity/rationale needed		
SACC	**SACC COMMENTS:** • The statement that discharges to air, water, sediment, land, and biosolids were all evaluated is misleading (NMP Risk Evaluation, p. 56). Water is the only ambient media considered in the environmental assessments in the NMP risk evaluation. • Consideration of environmental releases to water alone provides an inadequate picture of risk from NMP, as 99% of all environmental releases for NMP remain unassessed. Ten million pounds of chemical are unaccounted for, an amount representing over 70 times the releases modeled in the environmental exposures section. At a minimum, the evaluation should discuss, and preferably assess, all releases to water, soils, and the ambient atmosphere. • The decision to not further analyze aquatic exposures, based on a preliminary analysis that water releases were not expected to exceed concentrations of concern, limits the completeness of the risk evaluation. • Information on why individual media were dismissed from further evaluation is not provided. The rationale and the process used in deciding to	As described above, EPA has tailored the scope of the risk evaluation for NMP using authorities in TSCA Sections 6(b) and 9(b)(1). Section 1.4.2 of the final risk evaluation describes exposure pathways and risks that fall under the jurisdiction of other EPA-administered statutes or regulatory programs. The rationale for the selection of environmental compartments for assessment is also presented in the Problem Formulation document, as referenced in Section 1.4 of the risk evaluation. During problem formulation, EPA identified several pathways (including sediment, ambient water, land-applied biosolids, and ambient air) that did not require further analysis because environmental fate properties and first-tier analysis of environmental release data indicate that exposures are well below levels of concern. The statement cited in the first bullet point of the comment specifies that *during problem formulation* air, water, sediment, and biosolids were analyzed. As described in the problem formulation document, the air pathway was not further analyzed because inhalation exposure and bioaccumulation potential are expected to be low, and the solids pathways were not further analyzed because NMP is not expected to adsorb to suspended solids or sediment due to its high water solubility and estimated soil organic carbon/water partition coefficient (log K_{oc} = 0.9). EPA's conclusions about ambient air, ambient water, sediment, and land-applied biosolids are summarized in the

	exclude non-aqueous media from the environmental assessment should be further discussed in the risk evaluation.	Problem Formulation and in Section 4.6.2.3 of the risk evaluation. In the risk evaluation, EPA updated the screening level analysis for the ambient water pathway using surface water concentrations modeled based on 2018 TRI data. EPA evaluated potential risks for aquatic species by comparing surface water concentrations to concentrations of concern for aquatic species. EPA performed a screening level evaluation of potential human health risks by comparing exposures expected from incidental ingestion of surface water and dermal contact from swimming to human health points of departure.
SACC	**SACC COMMENTS:** • A clearer rationale is needed for the selection of modeled versus empirically measured data.	All data selections were made according to the *Application of Systematic Review in TSCA Risk Evaluations*. Under the systematic review guidelines, data sources are assigned overall quality scores based on strict and clearly defined criteria. While these criteria are different for measured and modeled data sources, the scoring system is designed to permit direct comparison between different types of data sources. In some cases this may lead to greater confidence being given to a model result (for instance, an output from one of the modules contained in the EPI Suite™ package) than to an empirical study whose design is lacking in one or more important aspects. Please refer to the Data Evaluation for detailed scores (with justifications) for individual data sources.
SACC	**SACC COMMENTS:** • Recommendation: Clarify the issues related to the assumed percent reduction of NMP discharges to POTWs in Table 2-1 and Appendix D. • The text regarding NMP transformation in publicly owned treatment works (POTWs) (NMP Risk Evaluation, p. 370) needs clarification. Table 2-1 indicates 45% reduction of NMP in POTWs, but in Appendix D, 92% removal is indicated. Data in Table D-2 suggest that the 45% value is used to	EPA revised Appendix E (previously Appendix D) describing POTW releases to surface water so as to clarify that the model input of 92% was used to estimate POTW removal of NMP for indirect dischargers.

	derive the information in the "PDM; input Loadings" column. A modification is reported in the stream concentration column that is difficult to follow, but could change the assumed use of the 45% value.	
SACC	**SACC COMMENTS:** • Recommendation: Clarify text regarding NMP transformation in POTWs (p. 370) to explain differences in NMP degradation that are listed in Table 2-1, Appendix D, and EPI Suite™ calculations. • One Committee member commented on the difference in the assumed fraction of NMP removed in wastewater treatment plants (WWTPs) as compared to assumed NMP removed in POTWs. It is difficult to follow the discussion in the text on Table 2-1, Appendix D of the draft risk evaluation and in the related Estimation Programs Interface Suite™ (EPI Suite™) calculations. It appears that the differences are the result of using different residency times for each type of facility in the EPI Suite™ runs. • Data in Table Apx D-2 suggest a median NMP degradation rate in activated sewage sludge of 17% in 24 hours and 61% in 120 hours. It seems reasonable to use the more robust 24-hour transformation rate estimate of 17% to describe NMP dissipation from POTWs instead of the 45% that appears to have been used in calculations. If this were done, the original hazard quotient (HQ) would be raised from 0.85 to 1.56 (0.85/0.45*0.87) and 1.85. Using this value and combining the effluent from the Oregon facilities, an HQ of 2.1 is	The POTW removal presented in Section 2.1.1 (>90%) was predicted by EPI Suite™ and is consistent with the value used for POTW removal as described in Appendix E (92%). Table 2-1 does not contain a value for POTW removal. It does contain the results of biodegradation studies, which are conducted under very different conditions from those present in a POTW and should not be viewed as equivalent. EPA updated Appendix E (previously Appendix D) to include 2018 reported data and made revisions to clarify that the NMP removal efficiency for wastewater treatment plants and for POTWs is the same at 92%. EPA was unable to replicate or identify the source of the degradation rate values cited in the third bullet. They do not appear in Table_Apx D-2.

	calculated. Using EPI Suite™ degradation estimates, the HQ would be larger.	
Water releases and exposures		
SACC	**SACC COMMENTS:** • Recommendation: Provide better estimates of the amount of NMP released to waters, or alternatively, consider increasing the estimate of releases to water to include all, or a substantial part, of the 1.4 million pounds of NMP unaccounted in the emission estimates. • The Committee had difficulty in tracking emissions and disposal amounts by media and type of disposal. Release data presented in Tables 1-3 and 1-4 do not line up. For 2017, Table 1-3 identified 10.4 million pounds of NMP releases, while Table 1-4 listed 1.53 million pounds to air, 7.55 million pounds to land, and 0.02 million pounds to water, leaving 1.4 million pounds unaccounted for. The unaccounted-for fraction is almost 2 orders of magnitude greater than that reported as discharge to water. In the absence of monitoring data to the contrary, with so little of total NMP discharges reported as releases to water and other media, and given that all other media are not being considered in this analysis, several Committee members concluded that it is reasonable and conservative to assume the unallocated fraction are water releases.	EPA's water release analysis uses TRI data to estimate the highest local per site water releases of NMP and is not intended to estimate overall releases. EPA does not expect any higher per site local water releases beyond those reported to TRI. EPA developed an approach and conducted a mass balance analysis for NMP. The analysis, which accounted for 83% of the NMP production volume and includes all releases reported to TRI, is summarized in Section 1.4.1 and details are provided in Appendix C.
SACC	**SACC COMMENTS:** Recommendation: Verify uncertainties in surface water concentrations (NMP Risk Evaluation, pp. 58, 59, and 370) and assumptions made regarding the fate of NMP in these surface waters by obtaining surface water monitoring data from public or private organizations	EPA obtained and considered reasonably available information, defined as information that EPA possesses, or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation. No surface water monitoring data were available. EPA gathered the amount of NMP released to surface waters as reported in TRI for 2015 for the draft

	through TSCA-provided authority.	risk assessment and then updated to include more recent, 2018 reported TRI data. Appendix E lists the facilities that discharge NMP directly to surface waters and the top 10 -12 facilities that discharge indirectly, that is, discharge to a wastewater treatment facility that discharges to surface waters after treatment. EPA estimated surface water concentrations using E-FAST 2014 model. This model is considered conservative as the estimated surface water concentrations consider receiving water dilution but do not include fate processes such as volatilization or biodegradation.
SACC	**SACC COMMENTS:** • Recommendation: Provide better justification for why so little environmental data covering only a small fraction of environmental releases of NMP were used in this draft risk evaluation. • The draft risk evaluation was limited to direct releases that enter surface water, which represent <0.2% of total releases (NMP Risk Evaluation, p. 369). This leaves >99% of NMP releases unassessed. The rationale for only assessing 12 discharge sites (NMP Risk Evaluation, p. 59) should be explicitly provided. • The risk evaluation should identify and discuss available monitoring data (at least at the point of discharge) from commercial users and producers.	EPA's water release analysis uses TRI data to estimate the highest site-specific water releases of NMP and is not intended to estimate overall releases. EPA included both direct dischargers and indirect dischargers (facilities that report transferring wastewater to another treatment facility such as a POTW) in both the draft and final risk evaluations. In addition, EPA updated the facility data as reported to TRI in 2018 to include all of the direct dischargers (8 facilities) and the top 12 indirect dischargers (representing 87% of total annual NMP discharges). If more than one facility discharged to a POTW the influent NMP mass was combined to estimate total NMP surface water concentrations. EPA developed an approach and conducted a mass balance analysis for NMP. The analysis, which accounted for 83% of the NMP production volume and includes all releases reported to TRI, is summarized in Section 1.4.1 and details are provided in Appendix C. Beyond releases reported to TRI, EPA did not identify any additional reasonably available environmental release or monitoring data for NMP.
SACC	**SACC COMMENTS:** • Recommendation: Consider discharges relative to stream flow volumes because the largest releases	EPA used the E-FAST 2014 model to estimate NMP surface water concentration resulting from facility discharges of NMP. Using the release data from TRI, including facility location, EPA

	may not present the largest ratios of discharge to stream flow. • Data that the Agency references for the NMP release amounts (NMP Risk Evaluation, Table D-1: Appendix D) are exclusively from the Toxics Release Inventory (TRI) database. TRI reports do not estimate releases as a proportion of stream flow. Stream flow data are potentially available from other sources, however. Provide releases per stream flow for (as many as practical of) the 124 facilities reporting releases. Estimating releases as a function of stream flow could provide additional insight into the impact of releases. It is unclear whether the largest absolute releases are not also the largest releases relative to stream flow, and hence also represent the highest exposure profiles for aquatic organisms. Reporting the discharge target waters would also be helpful.	could determine for some facilities the receiving waters, particularly if the facility had an associated National Pollutant Discharge Elimination System (NPDES) permit identification. The E-FAST model consists of a database of NPDES facilities and the corresponding receiving water stream flow data. Thus, the concentration of NMP in surface water is a function of the amount released over a given time period (12 days per year or 250 or 300 days per year) and the receiving water 7Q10 stream flow (*i.e.,* 7 consecutive days of lowest flow over a 10-year period). Thus, receiving water stream flow as well as the NMP discharge amount are both important factors EPA considered in estimating NMP surface water concentrations.
SACC; 64	**SACC COMMENTS:** • Recommendation: Add NMP releases to the single POTW from the two facilities co-located in Hillsboro and Aloha, OR to better estimate the highest potential water release estimates. Summing releases from facilities in Hillsboro (1,496 µg/L) and Aloha (499 µg/L) gives a predicted in-stream concentration of 1,995 µg/L, an increase of 33% in the value used for HQ determination. This increase would raise HQ for amphibians from 0.85 to 1.13 (0.85*1.33). This omission must be corrected. • One facility in the assessment discharged NMP-containing water to a treatment system that reuses partially treated water as process water (NMP Risk Evaluation, p. 370). The agency should state where	EPA has revised the risk evaluation to present updated discharges in 2018 and has revised the summary table to estimate the combination of the two facilities (Intel – Aloha Campus and Intel – Ronler Acres Campus) discharging to the same POTW (Rock Creek STP) in Hillsboro, Oregon. EPA updated the evaluation of risks to aquatic receptors using surface water concentrations estimated for the combine releases. While the RQ for the combined releases in 2015 was just over one, there were less than 20 days of exceedance. In addition, the combined releases based on the more recent 2018 TRI data did not result in an RQ greater than one. After updating the analysis in response to this comment, EPA did not identify unreasonable risks to aquatic receptors.

	this reused process water is discharged. If it returns to a POTW, then the modeled residual NMP would be estimated differently, specifically as 17% [0.15*(1+0.85*0.08)], rather than 15% as reported in the draft risk evaluation. **PUBLIC COMMENT:** • Table Apx D-2 indicates that Intel's Aloha and Hillsboro facilities discharge water to different POTWs. However, discharges from these facilities flow to the same POTW and should be combined in the table. • Intel has built a new onsite comprehensive wastewater treatment and recycling system at the Hillsboro facility that will greatly reduce future NMP discharges relative to the figures reported to TRI in prior years that are used in the draft risk evaluation. The new treatment facility became operational in 2019. Intel expects that by June 2020, all wastewater that might contain NMP at the Hillsboro facility will be treated onsite. Onsite NMP removal by the new wastewater treatment and recycling system is expected to equal or exceed the 92% NMP removal efficiency assumed by EPA for POTW treatment. Water treated at the onsite wastewater treatment and recycling system will then flow to the POTW, where it will be treated again and reduced by another 92%. Intel is collecting data to demonstrate the removal efficiency for NMP at the Hillsboro onsite treatment system and offered to share the data with EPA. • Applying the expected benefit of onsite wastewater treatment to 2015 TRI data, the estimated	

	concentration of NMP from the combined Hillsboro and Aloha facilities to the receiving body of water would be reduced from 1,995 to 619 µg/L. This demonstrates that on a going-forward basis, NMP releases from Intel's Oregon facilities will result in NMP surface water concentrations that are well below the threshold values assumed for purposes of the Agency's draft risk evaluation, and will not present an unreasonable risk to the environment.	
SACC	**SACC COMMENTS:** • The EPI Suite™ modeling used in this part of the assessment should not use the default of equal emissions to air, soil, and water but should be set appropriately for NMP. Applying the assumed release amounts to air and water into a standard level 3 fugacity model shows that partitioning from air into the water accounts for 1/3 to 1/2 of the NMP estimated to be discharged to water. This suggest that releases to water may be underestimated by 30-50%. This partitioning from air to water points out the significant inadequacy of evaluations that fail to include atmospheric emissions, especially when releases to the atmosphere dwarf those to water, as is the case with NMP. • Recommendation: Use the releases reported in the draft risk evaluation in EPI Suite™ modeling (Fugacity Level 3) rather than defaults of equal emissions to air, soil, and water.	No fugacity modeling was used in EPA's risk evaluation for NMP. As described in Section 2.3.2 and Appendix E, the surface water assessment relied on a combination of Toxics Release Inventory data and the Agency's Exposure and Fate Assessment Screening Tool (E-FAST). EPA believes this approach is more robust than relying on fugacity modeling to predict environmental concentrations.
SACC	**SACC COMMENTS:** • Recommendation: Discuss the potential for surface	EPA considered non-point source releases for the pathway of NMP remaining in land applied biosolids. EPA does not have

	runoff and other non-point source releases of NMP to water. • The focus on TRI reporting (NMP Risk Evaluation, p. 58) may have inadvertently excluded consideration of surface runoff and other non-point source releases of NMP to water.	specific monitoring data but based on NMP fate properties, EPA does not expect biosolids application and either migration through soil to groundwater or NMP runoff from subsequent precipitation to significantly contribute to NMP surface water concentrations. EPA was able to use facility-specific release date to quantitatively estimate NMP surface water concentrations. During problem formulation, EPA considered exposures from land-applied biosolids, one source of non-point source releases to water. Based on fate properties (described in more detail in response to the comment below) EPA concluded that no further analysis of this pathway was needed.
Fate		
SACC	**SACC COMMENTS:** • Recommendation: Add a discussion of land application of NMP and discuss the potential for movement to groundwater as well as the potential for degradation in subsurface soils. • NMP and its equitoxic major transformation products are known to be mobile and water soluble. Land application could provide a mechanism for movement to groundwater, much of which is not regulated/monitored under the Safe Drinking Water Act (SDWA). The Committee was provided no information on drinking water surveillance to confirm that this is not an issue. Two million pounds a year are disposed of in non-hazardous waste landfills and five million pounds in underground injection wells (NMP Risk Evaluation, Table 4-1). Yet, no data were provided on occurrence of NMP in groundwater, including near disposal facilities. Whether NMP degrades in the subsurface is an unanswered question.	As described in Sections 2.1.1 and 4.6.2.3 of the risk evaluation, EPA considered exposures from land-applied biosolids during problem formulation and concluded that no further analysis of this pathway was needed. In the NMP Problem Formulation, EPA explains that "NMP exhibits high water solubility (1000 g/L) and limited potential for adsorption to organic matter (estimated log Koc = 0.9); therefore, land releases will ultimately partition to the aqueous phase (*i.e.*, biosolids associated waste water and soil pore water) upon release into the environment. Because NMP readily biodegrades in environments with active microbial populations, NMP residues that remain following wastewater treatment are not expected to persist. NMP concentrations in biosolids-associated water are expected to decrease, primarily via aerobic degradation, during transport, processing (including dewatering), handling, and land application of biosolids (which may include spraying)." EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the

		scope of the risk evaluation for NMP using authorities in TSCA Sections 6(b) and 9(b)(1). As described in Section 1.4.2 of the risk evaluation, EPA did not include exposures via the drinking water pathway or disposal to underground injection, RCRA Subtitle C hazardous waste landfills, or RCRA Subtitle D municipal solid waste (MSW) landfills in this risk evaluation, as these exposure pathways fall under the jurisdiction of other EPA-administered statutes and associated regulatory programs.
SACC	**SACC COMMENTS:** • The risk evaluation should be consistent in how major fate processes are discussed. For example, the draft risk evaluation states that NMP does not persist in the environment and does not volatilize into the air, but later (NMP Risk Evaluation, p. 56) explicitly discusses releases to the atmosphere. • The aqueous persistence evaluation is missing an underlying citation in the primary literature. The citation in the draft risk evaluation is for the Agency Work Plan (EPA, 2015), but that document provided no underlying rationale for making this assertion.	Direct atmospheric releases and volatilization from surfaces can be thought of as distinct processes. The fate language is intended to describe general tendencies and should not be interpreted as categorically excluding these processes, only minimizing their relative importance. A citation regarding hydrolysis has been added to the narrative in Section 2.1.1.
Consider potential exposure to metabolites of NMP		
SACC	**SACC COMMENTS:** • Recommendation: Include major NMP degradation products (*e.g.*, N-methyl succinimide [NMS]) when estimating potential aquatic exposures. • The fate of major metabolites (a carbonyl compound and NMS, Chemical Abstracts Service Registry Number [CASRN] 1121-07-9) should be considered as part of the environmental fate discussion of the chemical. This could involve summing the estimated concentrations of the parent	A discussion of the fate of major NMP metabolites and degradants has been added to Section 2.1.1. Note that NMS (also called MSI) is primarily of interest as a metabolite of NMP and is not expected to persist as a degradant in the environment. As described in Section 2.1.1, while NMS is a potential product of atmospheric oxidation of NMP, it is likely transitory in the atmosphere, being subject to oxidation by hydroxyl radicals with an estimated half-life on the order of hours. Based on these properties, EPA does not expect NMP releases to the environment to result in substantial concentrations of NMS in surface water.

	and metabolites, and weighting them by relative toxicity. Not considering NMP metabolite (particularly NMS) concentrations in environmental media results in aquatic exposure estimates that are biased low. Measuring and summing the amount of these two analytes in discharge waters would improve understanding of aquatic environmental exposures to the combination of equitoxic NMP and NMS.	
Physical-chemical properties		
SACC	**SACC COMMENTS:** • Recommendation: Add to the Quality Review a discussion of the quality of estimates used for physical-chemical properties. Discuss methods to assess the quality of these data and why the estimates used were chosen over others available. • Recommendation: Add the Koa and dimensionless Henry's Law constant to the list of physical-chemical properties regularly reported in TSCA chemical evaluations.	Please see Supplemental File 1B for a complete summary of the data quality evaluation for physical and chemical properties. For the sake of conciseness and consistency with other Agency assessments, EPA prefers not to include K_{oa} and the dimensionless Henry's law constant, both of which can be calculated from the values provided.
SACC	**SACC COMMENTS:** • Table 2-1 (NMP Risk Evaluation, p. 57) lists the EPI Suite™ estimate of the indirect photolysis (photodegradation) half-life as 5.8 hours. This value is indicated as "estimated for atmospheric degradation" but may more appropriately be termed "photo-oxidation." It is also unclear whether this value is a half-life or an atmospheric lifetime.	The language in Table 2-1 has been revised for clarity.
SACC	**SACC COMMENTS:** • The term "sorption" should be used instead of "adsorption."	The document has been revised accordingly.

59	**PUBLIC COMMENTS:** • Full access to the three studies relevant to the fate of NMP in the environment is needed; the European Chemical Agency (ECHA) dossiers are cited (pp. 338-39).	EPA has replaced the ECHA study summaries by their respective primary sources: Shaver (1984) for the first, Gerike and Fischer (1979) and Křížek et al. (2015) for the second, and U.S. EPA (2012) (*i.e.*, EPI Suite™) for the third.
Climate change considerations		
34, 51	**PUBLIC COMMENTS:** • Elevated temperatures due to climate change are expected to influence vapor pressure, water solubility, and Henry's Law constants, and these scenarios should be considered in exposures where inhalation is considered. • Elevated temperatures due to climate change are likely to affect stream flow rates (15–30-year-old stream flow data were used to calculate surface water concentrations for NMP) and contaminant fate and transport. • To the extent that specific impacts of climate change are difficult to predict, EPA may account for that uncertainty through sensitivity analyses, a broader range of temperature-related assumptions, or additional UFs. Foreseen changes in temperatures and their impacts on the risk evaluation process must be considered by EPA in this risk evaluation.	Preliminary calculations indicate this temperature increase would increase vapor pressure by only 0.1%. Water solubility would increase to some extent, but NMP is already fully miscible at 25°C. NMP's enthalpy of solvation, needed to correct its air-water partition coefficient for an increase in temperature, is not readily available. However, without performing a sensitivity analysis, such a correction seems qualitatively unlikely to alter the conclusions of the fate assessment. For these reasons, an analysis of the influence of increasing temperatures on NMP exposures was not included in the risk evaluation.

3. Environmental Hazard and Risk Characterization

Environmental Hazard and Risk Characterization		
Charge Question 2.1: EPA determined that there are no environmental risks based on a screening level assessment of risk using environmental hazard data, TRI exposure data, fate information, and physical/chemical properties. Please comment on whether the information presented supports the analysis in the draft environmental hazard section and the findings outlined in the draft risk characterization section.		
#	**Summary of Comments for Specific Issues Related to Charge Question 2**	**EPA Response**
The committee was unable to review some data due to technical issues		
SACC	**SACC COMMENTS:** • Some toxicity data for aquatic organisms were not available to the Committee, and as a result, the quality and accuracy of the aquatic toxicity benchmarks could not be evaluated. • Weisbrod and Seyring (1980) cited in the NMP paint strippers work plan (EPA, 2015) was not in the reference list.	EPA remains committed to a transparent and reproducible systematic review process to ensure that the information the Agency relies on in its risk evaluations meets the scientific requirements in TSCA Section 26. EPA did provide access to all studies upon which the environmental risk evaluation was based. Access to the BASF and GAF studies were provided to reviewers through the HERO website. The peer review panel did not identify any issues with accessing this information either prior to or during the formal peer review panel meeting. In the paint stripper work plan document, Weisbrod and Sevring (1980) is cited in an appendix table based on information reported in OECD (2007), but is not included as a primary reference in the reference list. This citation was also not identified as part of the literature search and systematic review process for this risk evaluation.
Assessment Factors (AFs)		
SACC	**SACC COMMENTS:** • Recommendation: Increase the AF used in the calculation of the COC from daphnia toxicity data to 100 to account for limited acute and chronic testing and use of nominal levels in testing.	EPA acknowledges that there is uncertainty regarding the use of a single assessment factor to estimate hazards from chronic exposure to NMP. Additional context has been added to Section 4.3.4 of the final risk evaluation to describe the protectiveness of assessment factors. EPA acknowledges that several of the aquatic toxicity

	• The Committee was troubled that 4 of 5 studies used to establish environmental hazard were conducted at nominal concentrations, which are normally higher than actual test concentrations due to chemical losses to vaporization, sorption to test chamber walls, and transformation. • Daphnia appears to be the only species that was tested with chronic exposures. It is suggested that the numbers of aquatic species used for the acute and chronic assessments be specified on lines 133-136, 3787, and 3792 in the risk evaluation. • When chronic data are available for only one species, as for NMP, then the AF should be 100 to protect 93% of aquatic species (see Keinzler et al., 2017; Figure 8). Keinzler et al. (2017) also provides ratios for extrapolating daphnia toxicity to fish acute and chronic toxicities (also see Ahlers et al., 2009). • Use of a chronic AF of 10 rather than 100 may underestimate the risk that NMP poses to fish. Using an AF of 100, the chemical of concern (COC) would be 177 µg/L and the risk quotient (RQ) would be 8.5. This change, combined with underestimates of chemical concentrations, lead to an RQ estimate that approaches 20, even without accounting for the large underestimation of discharges to water noted by SACC in response to CQ1.	studies used nominal concentrations. This factor is considered in the systematic review process and data evaluation for the environmental hazard data. These studies were identified to be of sufficient quality for use in the RE. While an AF of 10 may not be protective for all chemicals and trophic levels, the use of 10 to calculate a concentration of concern for acute and chronic exposures to environmental receptors is consistent with existing EPA methodology for the screening-level assessment of new chemical substances. EPA is in the process of evaluating the body of reasonably available literature on the subject in order to determine whether to revise standards for application of AF and ACRs for the next 20 high-priority substances undergoing risk evaluation. EPA will consider the Keinzler et al., 2017 study in its assessment. Until the body of scientific evidence for assessment factors is evaluated, EPA will continue to use OPPT methodology as cited in the risk evaluation and apply an AF of 5 for acute and 10 for chronic aquatic invertebrate data.
SACC, 34, 51	**SACC COMMENTS:** • Recommendation: Clarify the selection of AFs and include UFs in the estimate of risks for aquatic organisms. • The assessment appears erroneous for aquatic receptors based on chronic toxicity data, due to the incorrect	Additional context has been added to uncertainty section 4.3.4 of the final risk evaluation to acknowledge the uncertainty associated with the use of AFs and ACRs. As described above, EPA is evaluating the body of reasonably available literature on the subject in order to determine whether to revise standards for application of AFs and ACRs for the next 20 high-priority substances undergoing risk

	application of AFs and failure to apply uncertainty factors (UFs). **PUBLIC COMMENTS:** • In absence of chronic data for fish, EPA divided the acute median lethal dose (LC50) by 10 to develop a chronic hazard value. EPA should apply a higher ACR or additional AFs, as recommended by SACC for 1-BP. A recent study of approximately 200 industrial chemicals reported a median fish ACR of 12.8, with a 90th percentile ACR of 102.4 and a maximum ACR of 1,370.6.	evaluation. EPA will consider the Keinzler et al., 2017 study in its assessment. Until the body of scientific evidence for assessment factors is evaluated, EPA will continue to use OPPT methodology as cited in the risk evaluation and apply an AF of 5 for acute and 10 for chronic aquatic invertebrate data.
SACC	**SACC COMMENTS:** • Several Committee members suggested that future TSCA chemical evaluations consider the use of Species Sensitivity Distributions in setting AFs. ○ It was noted that this requires toxicity evaluations on >5 organisms and is therefore not applicable to the current evaluation. • Adequate data to compute Species Sensitivity Distributions should be required for the next 20 chemicals scheduled for TSCA evaluation. • A member suggested that information about threatened and endangered species could help incorporate other UFs into the risk evaluation.	Thank you for the recommendation. EPA does use robust statistical methodologies including species sensitivity distributions when enough toxicity data are available for each taxonomic group. While insufficient data were available to do so for NMP, EPA will consider the use of species sensitivity distributions for the next 20 chemical undergoing TSCA evaluation, where possible. The TSCA risk evaluation focuses on exposures to particular species and environmental receptors, and appropriately considered impacts to affected species.
Conclusions on environmental risks - Scope of assessment		
SACC	**SACC COMMENTS:** • Recommendation: Provide a scientific or regulatory justification for why exposures and risks to terrestrial receptors should not be assessed. • The Committee concluded that statements regarding "no environmental risks" are misleading and must be modified. Only risks posed through surface waters were	During problem formulation, EPA identified several pathways (including sediment, ambient water, land-applied biosolids, and ambient air) that did not require further analysis because environmental fate properties and first-tier analysis of environmental release data indicate that exposures are well below levels of concern. As described in the problem formulation document, the solids pathways

	considered for environmental receptors in this draft risk evaluation. The NMP risk evaluation needs to be more specific in describing what risks were assessed and identifying what risks were expected but not assessed. • Terrestrial receptors should have been assessed (NMP risk evaluation, pp. 164-166) given the large amount of waste disposed in this manner. Terrestrial organisms are mentioned in the environmental hazards section (NMP risk evaluation, lines 3671-3673), but no further. Decisions made during problem formulation did not consider equitoxic transformation products of NMP when assessing potential risks to soil- and sediment-dwelling organisms.	were not further analyzed because NMP is not expected to adsorb to suspended solids or sediment due to its high water solubility and estimated soil organic carbon/water partition coefficient (log Koc = 0.9). EPA's conclusions about ambient air, ambient water, sediment, and land-applied biosolids are summarized in the Problem Formulation and in Section 4.6.2.3 of the risk evaluation. EPA considered transformation products of NMP, including biodegradation products and metabolites. As described in Section 2.1, based on qualitative analysis of reasonably available information, EPA concludes that these products are unlikely to pose risk to the aquatic environment. In the risk evaluation, EPA updated the screening level analysis for the ambient water pathway using surface water concentrations modeled based on 2018 TRI data. EPA evaluated potential risks for aquatic species by comparing surface water concentrations to concentrations of concern for aquatic species. Based on these analyses, EPA did not identify an unreasonable risk to environmental receptors from these pathways.
SACC	• The Committee determined that information presented was insufficient to support the conclusion that NMP does not present an unreasonable risk to environmental receptors through surface water exposure pathways. Issues that support this concern are: (1) the determination was based on limited chronic toxicity data; (2) only aquatic receptors were evaluated; (3) too small of an Assessment Factor (AF) was used (10 used instead of 100; see separate comment below); and (4) discharges to the same POTW were analyzed as separate events instead of a single larger discharge. These issues tend to	EPA has acknowledged the committee's concerns by adding additional context to Section 4.3.4 of the final risk evaluation to describe the uncertainty associated with the lack of chronic toxicity data, and the use of assessment factors (AFs) and acute to chronic ratios (ACRs). During problem formulation, EPA considered fate properties of NMP and performed a first tier analysis of environmental risks from NMP exposure through sediment, land-applied biosolids, and ambient air. EPA did not identify environmental risks from these pathways.

	support a conclusion of there being a reasonable probability of hazard to aquatic receptors from NMP exposures and that subsequent risk estimates are underestimated.	In response to the fourth concern, EPA updated the evaluation of risks to aquatic receptors using surface water concentrations estimated for the combined releases of the two facilities (Intel – Aloha Campus and Intel – Ronler Acres Campus) discharging to the same POTW (Rock Creek STP) in Hillsboro, Oregon. While the RQ for the combined releases in 2015 was just over one, there were less than 20 days of exceedance. In addition, the combined releases based on the more recent 2018 TRI data did not result in an RQ greater than one.
Data for determination of ecological hazard		
34, 51	**PUBLIC COMMENTS:** • The draft risk evaluation excludes the studies that demonstrate the greatest environmental risk, obscures the results of the studies that it does consider, and disregards risk quotients >100 times greater than EPA's unreasonable risk threshold. For aquatic invertebrates, EPA did not consider the most sensitive data, resulting in an underestimate of NMP's ecological risks. In the draft risk evaluation, EPA reports an EC_{50}/LC_{50} of 1,107–4,897 mg/L for aquatic invertebrates, based on a 1979 study of Daphnia magna. However, a 2004 study cited in the NMP Problem Formulation document reported an LC_{50} of 1.23 ml/L, approximately 1,000 times lower, for that same species. • EPA lacks adequate data to evaluate ecological risk. EPA does not have any studies of NMP's effects on terrestrial- or sediment-dwelling species, and no chronic aquatic toxicity data for NMP in fish. EPA should use its TSCA authority to collect or generate missing data on NMP's toxicity.	EPA obtained and considered reasonably available information, defined as information that EPA possesses, or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation. Given the timeframe for conducting risk evaluations on the first 10 chemicals, use of TSCA data gathering authorities has been limited in scope. In general, EPA intends to utilize TSCA data gathering authorities more routinely for the next 20 risk evaluations. During problem formulation, EPA considered fate properties of NMP and performed a first tier analysis of environmental risks from NMP exposure through sediment, land-applied biosolids, and ambient air. EPA did not identify environmental risks from these pathways. EPA remains committed to a transparent and reproducible systematic review process to ensure that the information the Agency relies on in its risk evaluations meets the scientific requirements in TSCA Section 26. EPA did provide public access to all studies upon which the draft risk evaluation was

	• Where data do exist, EPA has not provided public access to the studies that it relied on for its environmental risk evaluations (*e.g.,* study reports obtained from the NMP Producer's Group [BASF and GAF]), leaving the public unable to verify or critically evaluate EPA's conclusions.	based. Access to the BASF and GAF studies were provided through the HERO website. There were no NMP Producers Group studies used for evaluation of environmental hazard.
Consider toxicity of degradation products		
SACC	**SACC COMMENTS:** • Recommendation: Expand the discussion on the potential risk from NMS exposure to environmental receptors and include the lack of NMS concentration data in surface waters as a source of uncertainty in the evaluation of environmental risks. • The Committee expressed concern that the potential risk to aquatic organisms from exposure to NMS, a degradation product of NMP, is not discussed in the draft risk evaluation. Data suggest that NMS could be as toxic as NMP to daphnia.	*n*-methyl-succinimide (NMS) is a metabolite of NMP, but it is not expected to persist as a degradation product in the environment. As described in Section 2.1, while NMS is a potential product of atmospheric oxidation of NMP, it is likely transitory in the atmosphere, being subject to oxidation by hydroxyl radicals with an estimated half-life on the order of hours. Based on these properties, EPA does not expect NMP releases to the environment to result in substantial concentrations of NMS in surface water.
Cite Environment Canada reference		
SACC	**SACC COMMENTS:** • Recommendation: Include references to the Canadian determinations on bioaccumulation of NMP. • The draft risk evaluation states that NMP exhibits low potential for bioaccumulation (NMP risk evaluation, p. 58, line 977). One Committee member noted that Canada made a similar determination (Environment Canada, 1994), but that this seems to be in contradiction with toxicity data on microbiota (Campbell et al., 1999).	The NMP physical and chemical properties and environmental fate characteristics used in the RE are based on EPI Suite™ estimations and reasonably available fate data to characterize the environmental fate and transport of NMP. During problem formulation, EPA also analyzed the air, water, sediment, land and biosolids pathways. These results are described in the NMP Problem Formulation document (U.S. EPA, 2018). EPA identified and evaluated environmental fate data quality studies according to the TSCA systematic review process. Environmental fate data from acceptable studies were extracted and integrated during risk evaluation. Based on the results obtained from the data quality evaluation process EPA has high confidence in the studies used to characterize the environmental fate of NMP. This data may or may not be included in the Canadian

		assessment.
Modeling issues		
SACC	**SACC COMMENTS:** • Recommendation: Include confidence bounds for E-FAST predicted concentrations and reduce the number of significant digits reported in tables and text from 4 to 2, based on precision of input values. • The E-FAST model predicted concentration (1,496 µg/L) is close to the chronic value of 1,768 µg/L. The Committee recommended including estimates of upper and lower 95% confidence limits on model-estimated values to help assess if these two values are statistically the same.	EPA has revised the surface water estimates to reduce the number of significant figures. EPA used the E-FAST model to predict site-specific stream concentrations of NMP given TRI releases. However, EPA also used the Probabilistic Dilution Model (PDM) portion of E-FAST 2014 for free-flowing water bodies. The PDM predicts the number of days/yr a chemical's COC in an ambient water body will be exceeded. COCs are threshold concentrations below which adverse effects on aquatic life are expected to be minimal. PDM calculates the COC exceedance probability using a stochastic procedure developed by Di Toro (1984). This approach requires the means and coefficients of variation of stream flow, effluent flow, and effluent concentration as input. Mean stream flow and mean effluent flow are provided by the E-FAST2 Main Facility File. The stream flow coefficient of variation is estimated using the mean stream flow, low stream flow (7Q10, also available in the E-FAST2 Main Facility File) and empirically derived coefficients specific to each subbasin that are available in the Basin Coefficient Statistical File. The coefficients of variation of effluent flow and concentration are assumed to be 0.24 and 0.85, respectively. Following entry of chemical loading and the COC, the probability of exceedance is calculated by PDM using the Di Toro algorithm. PDM does not estimate exceedances for chemicals discharged to still waters, such as lakes, bays, or estuaries. For these water bodies, the days of exceedance is

		assumed to be zero unless the predicted surface water concentration exceeds the COC. Additional details of the E-FAST model are found at: https://www.epa.gov/sites/production/files/2015-04/documents/efast2man.pdf EPA did not have enough chronic toxicity data available to make a statistical comparison of the chronic COC with the estimated surface water concentration using confidence intervals. Instead, in scenarios with limited data, EPA picks the lowest (most sensitive) toxicity value and divides by an assessment factor of 10 to determine the chronic COC. There is uncertainty associated with the use of assessment factors (*e.g.*, what value is large enough to be protective) which has been added as a discussion in Section 4.3.4.
RQs ~ 1		
SACC	**SACC COMMENTS:** • Several Committee members noted that the RQ for the chronic (environmental) risk scenario (NMP Risk Evaluation, Table 4-2, p. 209) is very close to one. RQs approaching 1 are likely to be very sensitive to small changes in estimates of maximum exposure concentrations and/or COCs. • Recommendation: Flag RQs close to 1 for further evaluation because they are sensitive to small changes in the estimates of exposure concentrations and/or COCs.	EPA has revised the risk evaluation and re-calculated RQs corresponding to the updated surface water estimates from 2015 and 2018 TRI data (Table 4-2 and Table 4-3). All acute and chronic RQs < 1 except for the POTW (Rock Creek STP) in Hillsboro, Oregon, where the RQ was 1.1. The RQ increased from the Draft RE and reflects the combination of the two facilities (Intel – Aloha Campus and Intel – Ronler Acres Campus) that discharge to the same POTW, as was suggested by the committee. Because frequency and duration of exposure also affects the potential for adverse effects in aquatic organisms, the number of days that the chronic COC was exceeded was also calculated using E-FAST as described in Section 2.3.2. Facilities with an RQ ≥ 1 for the acute risk scenario or an RQ ≥ 1 and 20 days or more of exceedance for the chronic risk scenario would suggest the potential for environmental

		risks posed by NMP. The 20-day exceedance time frame was derived from partial life cycle tests (*e.g.*, daphnid chronic and fish early life stage tests) that typically range from 21 to 28 days in duration. Because the surface water concentration at Hillsboro was predicted to exceed the chronic COC for 2 days per year, risk from chronic exposure was not indicated for aquatic receptors.
Exposure data used for ecological risk characterization		
32	**PUBLIC COMMENTS:** • EPA used its E-FAST model to predict surface water concentrations at the TRI/DMR facilities based on facility-specific emissions and wastewater treatment removal. The Probabilistic Dilution Model (PDM) was used to predict the number of days a stream concentration may exceed the designated concentration of concern. It is unclear whether EPA used the dilution factor for the site-specific receiving water body or the national 7Q10 dilution factor, which is equivalent to 1.0. EPA should clarify the reasoning for using the 7Q10 value for the facility-specific receiving water body associated with the facilities discharge, rather than the E-FAST PDM 7Q10 for dilution.	EPA uses the 7Q10 hydrologically based low flow in several program offices, including the NPDES permit writing program. The 7Q10 is the lowest 7-day average flow that occurs (on average) once every 10 years. The hydrologically based low flow is computed using the single lowest flow event from each year of record, followed by application of distributional models (typically the Log Pearson Type III distribution is assumed) to infer the low flow value. National Pollutant Discharge Elimination System (NPDES) permit writers often need to calculate low flow statistics for reasonable potential analyses and water quality-based effluent limitation (WQBEL) calculations or to confirm estimates provided by the permittee during the NPDES permit development process. The EPA E-FAST model also uses the accepted 7Q10 low flow to estimate site-specific NMP stream concentrations at facilities reporting NMP releases. The Probabilistic Dilution Model (PDM) is used for predicting downstream chemical concentrations from an industrial discharge. It calculates the probability that a given target stream concentration will be exceeded, and the number of days per year the exceedance condition will exist. The calculation of probability assumes that receiving stream flow, effluent flow, and effluent concentration are log-

		normally distributed. The statistics involve both the arithmetic and logarithmic forms of the mean and coefficient of variation (., standard deviation/mean) for the flow and concentration of both the stream and the effluent. PDM can predict frequency of exceedance of the concern concentration in streams that have a record of flow data from gaging stations as well as in streams without gaging stations. Detailed information on the E-FAST model is publicly available at: https://www.epa.gov/sites/production/files/2015-04/documents/efast2man.pdf
54	**PUBLIC COMMENTS:** • EPA applied a number of conservative estimates in evaluating environmental exposures in the draft risk evaluation, particularly regarding surface water concentrations (*e.g.,* 12- and 250-day acute and chronic release scenarios). These conservative assumptions may be suitable for a "first-tier" exposure assessment, but EPA should more clearly articulate what approach(es) it would use for higher tier environmental exposure estimates and justify assumptions regarding release scenarios. Further, since EPA is estimating exposures at specific facilities using this approach, it should understand and incorporate those facility-specific conditions into its assessment.	The "first-tier" or conservative screening level analyses for risks to aquatic organisms did not identify risks for any of the direct or indirect dischargers of NMP reporting to the TRI in 2015 or 2018. These results do not indicate the need for any further detailed environmental risk analyses.
54, 46	**PUBLIC COMMENTS:** • EPA needs to be more transparent about how it will analyze environmental risks that are already subject to EPA regulation under other environmental laws when conducting risk evaluations. It is recommended that EPA more clearly explain its approach, consider whether its approach is consistent across its TSCA risk evaluations, and if not, to explain why not. For example, EPA should	As described in Section 1.4.2, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA believes that coordinated action on exposure pathways and risks addressed by other EPA-administered statutes and regulatory programs is consistent

	address when TRI estimates are adequate to predict concentrations in air, water, and land, and when they are not, in addition to what constitutes adequate "regulation" under other environmental laws and regulation within EPA's purview, providing justification when EPA will either not analyze it further or not review it at all in a risk evaluation. Differences in treatment of NMP and methylene chloride (MC) illustrate the problem. MC is a regulated priority pollutant under the Clean Water Act (CWA) with CWA monitoring data and CWA technology-based standards, but EPA decided to analyze the ambient water pathway anyway. For NMP, however, which is not regulated under CWA and has no monitoring data, EPA dropped the ambient water pathway based on estimated TRI release data.	with statutory text and legislative history, particularly as they pertain to TSCA's function as a "gap-filling" statute, and also furthers EPA aims to efficiently use Agency resources, avoid duplicating efforts taken pursuant to other Agency programs, and meet the statutory deadline for completing risk evaluations. EPA has therefore tailored the scope of the risk evaluation for NMP using authorities in TSCA Sections 6(b) and 9(b)(1). During problem formulation, EPA performed a first-tier screening analysis of risks from ambient air, ambient water, sediment, and land-applied biosolids. EPA did not identify risks from human or environmental exposures that may result from these pathways. In the final risk evaluation, EPA updated the evaluation of risks to aquatic life and the general population from ambient water exposures using more recent TRI release data. As described in Section 4.1, EPA did not identify risks to environmental receptors or the general population from ambient water.

4. Occupational and Consumer Exposure

Occupational and Consumer Exposure		
Charge Question 3.1: Please comment on the reasonableness of the characterization of occupational exposure for workers and occupations non-users. What other additional information, if any, should be considered. **Charge Question 3.2:** Please comment on the transparency of EPAs approach and the assumptions EPA used to characterize exposure for ONUs. **Charge Question 3.3:** Please comment on the approaches and assumptions used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving the workplace exposure assessment. More specifically, if other sources of monitoring data are available to estimate air concentrations for worker exposures, please provide specific citations. **Charge Question 3.4:** Please comment on assumptions used in the absence of specific exposure information (*e.g.*, dermal surface area assumptions: high-end values, which represents two full hands in contact with a liquid: 890 cm2 (mean for females), 1070 cm2 (mean for males); central tendency values, which is half of two full hands (equivalent to one full hand) in contact with a liquid and represents only the palm-side of both hands exposed to a liquid: 445 cm2 (females), 535 cm2 (males)). **Charge Question 3.5**: Please comment on EPAs approach to characterizing the strengths, limitations and overall confidence for each occupational exposure scenarios presented in Section 2.4.1. Please comment on the appropriateness of these confidence ratings for each scenario. Please also comment on EPAs approach to characterizing the uncertainties summarized in Section 2.4.1.4. **Charge Question 3.6:** Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of consumer inhalation exposure, including specific citations of data sources characterizing consumer emission profiles of NMP-based products. **Charge Question 3.7:** Please comment on EPAs approach to characterizing the strengths, limitations and overall confidence for each consumer exposure scenarios presented in Section 2.4.2. Please comment on the appropriateness of these confidence ratings for each scenario. Please also comment on EPAs approach to characterizing the uncertainties summarized in Section 2.4.2.6.		
#	**Summary of Comments for Specific Issues Related to Charge Question 3**	**EPA Response**
Dermal absorption and exposure from direct skin contact with liquids		
SACC	**SACC COMMENTS:** • Recommendation: Revisit dermal absorption modeling and adopt a matrix of standardized approaches based on conditions of use, the physical-chemical properties of the agent of interest, and its vehicle (if any).	Modeling of dermal absorption of NMP is captured in the PBPK model and differs from dermal absorption modeling applied in other TSCA risk evaluations. The NMP risk evaluation does not cite Frasch and Bunge (2015) or Frasch (2011). This comment appears directed at the dermal modeling approach applied in TSCA risk evaluations for

	• In the draft risk evaluation, the Frasch and Bunge (2015) model is cited and used rather than the Frasch et al. (2011) model that was used in previous risk evaluations. The Frasch and Bunge (2015) model deals with disposition of skin depot left behind after skin decontamination but does not address disposition of total applied dose. This is considered as misuse of the Frasch and Bunge (2015) model. • The draft risk evaluation links to CEM 2.1, which includes 4 dermal models, while previous evaluations linked to CEM 2.0, which included 3 dermal models (model identified only as "CEM" in the evaluations). This may lead to confusion. The risk evaluation needs to clearly identify the actual model used and consider assigning version numbers to models in a consistent and standardized manner.	other chemicals. EPA is currently reevaluating its approach to dermal exposure modeling for TSCA risk evaluations. The NMP PBPK models incorporate reasonably available NMP-specific data on dermal absorption. For example, reasonably available data demonstrate that dermal permeability of neat NMP is higher than permeability of 50% NMP in water. The PBPK model used to model human exposures in the final risk evaluation adjusts dermal permeability based on the weight fraction of NMP in products associated with each exposure scenario. While the solvents present in NMP containing-products may influence dermal absorption, EPA does not have data on the impact of the specific solvents and product formulations relevant for each condition of use on the dermal permeability of NMP. EPA used CEM 2.1 and checked that the links are appropriate.
SACC	**SACC COMMENTS:** • Recommendation: Exposure factors should more adequately reflect uncertainty and avoid use of excessive significant digits. • EPA used hand area as a surrogate for exposed skin. One Committee member noted that information from occupational agriculture is supportive of the idea that hands are disproportionately exposed as a result of normal human behavior and that hand area was therefore a reasonable starting point. It was thought, however, that EPA estimates to three significant digits were unrealistically precise. It was suggested that hand area represents an exposure factor for which use of distributed values rather than point estimates would be relatively easy to implement. It was also noted that surveyed	EPA uses three or more significant digits only when reporting or using values reported in literature sources and in its guidance documentation. For example, EPA's modeling guidance documents specify surface area input values that have three significant digits, and EPA reports these values consistently in its first 10 risk evaluations. EPA presented all occupational PBPK modeling results with two significant figures in Section 2.4.1.3. EPA clarified in Section 2.4.1.1 that EPA has no reasonably available information on actual surface area of contact with liquid and that the assumed values represent adequate surrogates for most uses' central tendency and high-end surface areas of contact with liquid that may sometimes include exposures to much of the hands and also beyond the hands, such as wrists, forearms, neck, or other parts of the

	graffiti removers self-reported exposure to skin other than hands.	body. EPA accounts for distributed values using the central tendency and high-end assumptions for surface areas.
32, 49, 52, 54, 56, 31, 64	**PUBLIC COMMENTS:** • In the draft risk evaluation, EPA's default assumption is that the total skin surface area of hands is in prolonged contact with the liquid product. This assumption is inaccurate, does not reflect the actual work activities, and does not take into consideration information provided to EPA detailing engineering controls and chemical handling procedures that explicitly prevent dermal contact with liquid NMP or other forms of residual NMP. The low NMP concentrations at semiconductor facilities during routine or maintenance tasks are not indicative of the presence of liquid NMP, and are therefore inconsistent with EPA's assumption of extensive dermal contact. While an Intel employee may periodically touch liquid NMP while wearing personal protection equipment (PPE), such contact would be brief and the employee's hands would never be immersed in liquid. Accordingly, the chronic exposure scenario used in the draft risk evaluation is not reflective of Intel's work practices and exposure potential for conditions of use in the semiconductor industry. This assumption results in exposure scenarios driven by dermal contact with the liquid. For example, in the electronics industry, in most scenarios presented, 100% of the area under the curve (AUC) (*i.e.*, internal dose) is due to dermal contact, including tasks such as maintenance, truck unloading, and fabrication). Justification for these exposure assumptions for these occupational scenarios is needed. • Immersion of one or two hands in concentrated or neat NMP solvent for prolonged periods is implausible, as it	EPA has improved and clarified dermal input parameter assumptions in Section 2.4.1.1. EPA clarified in Section 2.4.1.1 that the exposure duration assumptions of full-shifts for high-ends account for the possibility of repeated contact with NMP such that NMP does not fully volatilize from the skin before the next contact event, potentially resulting in prolonged exposure. EPA has expanded the range of contact durations for OESs where values of both shift durations and task durations were reasonably available. EPA clarified in Section 2.4.1.1 that EPA has no reasonably available information on actual surface area of contact with liquid and that the assumed values represent adequate surrogates for most uses' central tendency and high-end surface areas of contact with liquid that may sometimes include exposures to much of the hands and also beyond the hands, such as wrists, forearms, neck, or other parts of the body. EPA clarified in Section 2.4 that non-immersive dermal contact with liquid films is evaluated. In the Electronics Manufacturing OES, EPA includes 6 worker activities within semiconductor manufacturing. EPA added several PBPK model runs using semiconductor industry-proposed input values and data including assumed contact durations. EPA has not found reasonably available data on actual contact durations or contact surface area for workers in the semiconductor industry and most other OESs.

	is a skin irritant that can cause dermatitis, blistering, or cracking (E.U. SCCS, 2011) that would be difficult to tolerate for prolonged periods of time (one or two hands immersed in solvent for 30 or 60 hours/week, respectively). • The semiconductor worker scenarios are characterized by margins of exposure (MOEs) >30 when dermal liquid contact is assumed to be negligible. Thus, the draft agency "unreasonable risk determination" for semiconductor workers is highly sensitive to the unsubstantiated assumption of extensive and immersive skin contact with liquid NMP. ○ An assumed condition of use with immersive and prolonged contact with NMP is inconsistent with the statement in the 2016 peer-reviewed publication that "human exposures to NMP will be primarily via the inhalation route" (Poet et al., 2016, Sup. A1, p. 5). EPA has not provided a transparent substantiated analysis in the 2019 draft risk evaluation explaining the inconsistency in the stated contribution of liquid contact between the peer-reviewed paper and the draft TSCA evaluation. ○ The unexpected dominant contribution of NMP contact with the skin to internal exposure should have resulted in additional steps by the Agency to characterize uncertainty and refine model assumptions. • EPA must include appropriate justification of dermal exposure assumptions for occupational scenarios in the draft risk evaluation and better represent the occupational exposure scenarios experienced by workers for both central tendency and high-end scenarios. Table 4-49 indicates that 52 of the 58 exposure calculations were	EPA added discussion in Section 2.4.1.1 regarding the relative contributions of each exposure pathway to total exposures, which vary according to parameter values for NMP weight fraction in the liquid product contacted, skin surface areas in contact with the liquid product and with vapor, durations of dermal contact with liquid product and with vapor, air concentration for inhalation and vapor-through-skin exposure, body weight of the exposed person, and glove protection factor and respirator assigned protection factor (if applicable). In scenarios where the three parameters involving dermal contact with liquid product (NMP weight fraction in the liquid product contacted, skin surface areas in contact with the liquid product and with vapor, durations of dermal contact with liquid product) have relatively high values, this route can be the dominant route for worker exposures. To illustrate the contribution of inhalation and vapor-through skin versus dermal contact with liquids, the male worker and male ONU AUC values can be compared for the same work activity for an OES because the PBPK inputs for both workers and ONUs utilize the same NMP air concentration, while the worker PBPK inputs include parameters for dermal contact with liquid and the ONU PBPK inputs assume no dermal contact with liquid. For example, for the OES Laboratory Use, the central tendency scenario (PF = 1) results are a male worker AUC of 77 hr-mg/L and male ONU AUC of 0.023 hr-mg/L. These results indicate a 0.03% contribution from inhalation and vapor-through-skin exposure and a 99.97% contribution from dermal contact with liquid for the worker. For the same OES, the central tendency scenario (PF = 20) results are a male

	driven entirely by the dermal exposure levels (>88% NMP exposure resulting from the dermal route). Because the dermal route has an outsized effect on the overall exposure – and consequently the risk determination – EPA should ensure that these values are as accurate as possible, rather than relying on overly conservative assumptions.	worker AUC of 3.4 hr-mg/L and male ONU AUC of 0.023 hr-mg/L (unchanged because no ONU dermal exposure). These results indicate a 0.68% contribution from inhalation and vapor-through-skin exposure and a 99.32% contribution from dermal contact with liquid for the worker. These results show that, with decreasing dermal exposure to liquid, inhalation and vapor-through-skin exposure have an increasing contribution to exposure results. For the same Laboratory Use OES, the high-end scenario (PF = 1) results are a male worker AUC of 400 hr-mg/L and male ONU AUC of 0.86 hr-mg/L. These results indicate a 0.22% contribution from inhalation and vapor-through-skin exposure and a 99.78% contribution from dermal contact with liquid. Compared with the central tendency (PF = 1) scenario, the NMP air concentration increased by >4000% and contact duration and hand surface area increased by 100%. The exposure results between the central tendency and high-end scenarios show higher contributions from inhalation and vapor-through-skin exposure; however, the increase in the contributions of these pathways is not proportional to increase in air concentration. For this OES, regardless of central tendency or high-end and PF, dermal contact with liquid is the dominant pathway for workers. EPA believes that engineering controls would not impact contact duration with liquids but would generally reduce air concentrations. Such reductions would be reflected in air monitoring data. EPA considers chemical handling practices by reflecting different worker activities in each OES to the extent that these activities are known.

		EPA does not expect that NMP air concentrations correlate to dermal contact, which is indicated by worker activities. EPA accounts for potential glove use by applying a range of glove protection factors for every worker activity modeled as indicated in Section 2.4.1.1. The modeling results for each OES central tendency and high-end scenario are presented in Table 2-77 and for all scenarios for all OESs in the Supplemental Excel File on Occupational Risk Calculations. EPA does not have reasonably available data or information to inform specific durations of contact and associated concentrations and formulations that would be implausible or cause toleration issues.
SACC, 31, 49, 52 53, 56, 54, 64	**SACC COMMENTS:** • Assumptions regarding work shift duration, specifically the assumption that central tendency exposures involve durations <8 hours seem unrealistic and should be reassessed. • The draft risk evaluation should consider assuming longer work-days for some workers since 12-hour shifts were noted in the literature for degreasing of optical lenses (Xiaofei et al., 2000) and as reported in the sampling data from SIA (2019). • Recommendation: Revisit shift duration assumptions or explain why results are not sensitive to that parameter. **PUBLIC COMMENTS:** • Table 2-32, p. 102 in the draft risk evaluation and Table 2-42, p. 84 of the Supplemental Information of the NMP Draft Risk Evaluation report exposure durations for several tasks that are incorrect. For example, EPA made an incorrect assumption that semiconductor industry workers could be exposed to NMP throughout their	EPA clarified in Section 2.4.1.1 that shift durations are assumed to be 8 (standard) or 12 hours, depending upon available data, and that durations of contact with liquids are based on fractions of shift-durations or other assumptions (*e.g.,* task durations). EPA does not assume any shift durations < 8 hours. EPA assumes 12-hour shifts for several subgroupings of the Electronics Industry OES where air monitoring data indicates such durations. Therefore, EPA revised shift durations based on reasonably available data. EPA does not have reasonably available data or information that shows assumed exposure durations for dermal contact with liquids to be incorrect for any tasks. EPA added several PBPK model runs using semiconductor industry-proposed input values and data including their assumed contact durations. EPA has not found reasonably available data on actual contact durations or methods for measuring these durations for workers in any industry, including the semiconductor industry.

	entire work shift (8-12 hours), rather than episodically. However, no individuals in semiconductor manufacturing handles containers for 6-12 hours/day. Although Intel factory shifts range up to 12 hours and a given maintenance activity may take several hours, the actual time any worker would come into contact with NMP (always while wearing PPE) would be only a small fraction of this time. For most maintenance tasks, contact would be short; potential for chemical contact would typically be between 15 and 60 minutes (except in very unusual circumstances, such as if cleaning up a small spill contained within complex equipment). • Page 128: it is incorrectly assumed that truck unloading at semiconductor sites is a 4- or 8-hour/day task. Data submitted by SIA (2019) indicate that the task takes 2-4 hours and is performed no more than 2 times each year. • In the lithium ion battery industry, employees prepare batches 1-2 times/day, 3-4 times/week, with a duration of 2.5 hours per batch. • Page 132, Table 2-66: The task durations for semiconductor applications are inaccurate. • The frequency and duration assumptions in the draft risk evaluation did not consider the duration and frequency of use data provided to EPA from semiconductor fab facilities including worker exposure monitoring for NMP conducted at 14 facilities with a total of 118 samples and is not reflective of the actual work activities. It is requested that EPA reconsider their estimated duration of potential exposure and take into consideration the data provided to them. Many tasks involve episodic handling of NMP and task duration is short. • The current dermal liquid contact exposure assumptions are based primarily on a policy rather than a "best	EPA clarified in Section 2.4.1.1 that the contact duration assumptions of full-shifts for high-ends account for the possibility of repeated contact with NMP such that NMP does not fully volatilize from the skin before the next contact event, potentially resulting in prolonged exposure. In this section EPA also clarified that where available, EPA utilized exposure durations from the available task-based inhalation monitoring data for generating what-if type exposure scenarios assuming that the workers were contacting NMP-containing liquids over only the monitoring duration (*i.e.,* the entire task duration). Task-based duration estimates do not account for either liquid remaining on the skin after the task is completed or for workers performing a task multiple times during their shift. EPA *expanded* PBPK runs using both shift-based and task-based duration estimates for many OESs. EPA did not assume that truck unloading at semiconductor sites is a 4- or 8-hour/day task but assumed shift-based durations for central tendency and high-end estimates and task-based durations for what-if estimates. EPA removed the truck unloading from chronic estimates since this task is not performed 4 or 5 days per week. EPA used the most recent industry-provided task duration estimates in some PBPK runs for the lithium ion battery industry and for the semiconductor applications, including fab facilities. EPA's current dermal liquid contact exposure assumptions are based on the "best available science" approach and have considered detailed information supplied by the assessed industry, including industry-proposed parameter values as

	available science" approach that considered detailed information supplied by the assessed industry. The equations used by EPA imply immersion for prolonged periods of time. Rather than a generic assumption of immersion in NMP-containing liquid, the dermal exposure chapter of the American Industrial Hygiene Association (AIHA) reference text "Mathematical Models for Estimating Occupational Exposures to Chemicals, 2nd Edition" advises that scenario-specific liquid loading, surface area, and contact time should be determined based on the conditions of use. The chapter notes that "a far more realistic scenario is to consider a finite volume of chemical deposited on the skin that is subsequently removed by one or more mechanisms, such as washing or evaporation" (Sahmel et al., 2009, p. 119). It is implausible that hand surface area of liquid NMP contact and fraction of the shift exposed to liquid be the same in dissimilar industries such as paint, coatings, adhesives, and semiconductor manufacturing, which EPA grouped together. • Many tasks involve the use of NMP in well-ventilated spaces with conditions favoring the evaporation of incidentally generated solvent residual. As described in Sahmel et al. (2009), the consideration of evaporation of volatile or semi-volatile chemicals from the skin is an important determinant of dermal exposure potential. • At least one peer-reviewed approach capable of using scenario-specific factors is available for dermal liquid exposure assessment. The IH SkinPerm model is freely available from AIHA (https://www.aiha.org/public-resources/consumer-resources/topics-of-interest/ih-apps-tools) and presented in the peer-reviewed literature in Tibaldi et al. (2014). This model allows for consideration	well as additional parameter values that consider more factors, such as repeated contact with liquids during the workers' shifts and time for NMP-containing liquids to evaporate. EPA's approach is consistent with the dermal exposure chapter of the American Industrial Hygiene Association (AIHA) reference by using scenario-specific surface area and contact time that are determined based on the conditions of use. The liquid loading aspect covered in AIHA's dermal chapter and in AIHA's IH SkinPerm model is handled differently because PBPK modeling for internal dose does not use a liquid loading parameter as do the more simplistic potential dose models covered by the AIHA reference. EPA clarified in Section 2.4 that non-immersive dermal contact with liquid films is evaluated. EPA does not have reasonably available data to indicate dissimilarity of industries grouped into OESs. EPA did not group paint, coatings, adhesives, and semiconductor manufacturing into an OES. Regarding AIHA's IH SkinPerm model contact time (h) based on a consideration of evaporation, this model's treatment does not account for repeated contacts during a worker's shift, task duration, nor worker activities for particular NMP OESs and COUs. Therefore, the evaporation-based contact times estimated by this AIHA model are less useful for EPA's risk evaluation. EPA considers evaporation of volatile or semi-volatile chemicals from the skin as a determinant of dermal exposure potential by using contact duration. This evaporation is only one of many determinants toward contact duration.

	of realistic exposure scenario factors including skin surface loading (mg/cm^2) and contact time (h) based on a consideration of evaporation. EPA should explore application of this model to the NMP risk evaluation. • EPA does not specify the loading of NMP on the skin or gloves because a scenario equivalent to skin immersion in solvent was assumed. Research has shown that the amount of substance deposited on the skin or gloves can vary by activity (Sahmel et al., 2009). The AIHA dermal exposure assessment chapter suggests default dermal loading of 0.7-2.1 mg/cm^2 for incidental contact with liquids (Sahmel et al., 2009). The tasks described by SIA (2019a) indicated very limited contact opportunities of NMP with skin or gloves. Thus, it is reasonable to assume that the maximum daily loading of NMP-containing liquid during a work-shift is approximately 0.7-2.1 mg/cm^2. • Cardno ChemRisk used IH SkinPerm (Tibaldi et al., 2014) to determine reasonable contact times for NMP. The model indicated times to complete evaporation of 20 and 60 minutes when the loading was 0.7 and 2.1 mg/cm^2, respectively. This conclusion was insensitive to surface area over the range of 10-1,000 cm^2. Cardno ChemRisk confirmed that the dermal permeability constant used by EPA of 4.78x10^{-4} was similar to the value of 3.66x10^{-4} predicted by the algorithm of IH SkinPerm; thus, predictions of dermal absorption were similar in both methods.	Scenario-specific factors available for dermal liquid exposure assessment in the IH SkinPerm model are not specific enough to specifically determine surface area of contact, the number of repeated contacts during a worker's shift, task duration, or worker activities for particular NMP OESs and COUs. Therefore, parameters estimated by this AIHA model are less useful for EPA's risk evaluation. To address dynamic loading on the skin (*i.e.*, where deposition is defined by an amount/area/time deposited) or exposure to very thin films would require significant revision of the PBPK model. It is likely that for a film on exposed skin on the order of microns of thickness (1.02 mg/cm^2 is equivalent to a layer 10 μm thick), evaporation will become a significant factor, with that evaporation being temperature dependent. A film on exposed skin will be simultaneously warmed by body heat and cooled by evaporation. The U.S. EPA is not aware of a PBPK model of dermal exposure that accounts for the complex interplay of these factors; *i.e.*, such a model is not in the realm of available science. On the other hand, if NMP penetrates under a protective glove, that film would not be subject to evaporation and EPA is not aware of science to indicate that absorption would vary as a function of the film thickness, as long as it was present. Therefore, EPA considered two options: making the best possible use of the Poet et al. PBPK model (with minor corrections) or performing the risk assessment without a PBPK model. The use of the PBPK model under the assumption that the exposed skin is effectively immersed in NMP was considered the preferred option, making use of the best available science, despite its limitations.

		Unlike EPA estimates of contact durations, the Cardno ChemRisk analysis equates evaporation time to contact durations, which does not account for extended, continued contact or repeated contacts over a shift.
SACC	**SACC COMMENTS:** • SACC expressed concern that glove protection factor (GPF) assumptions made by EPA were overly optimistic and unsubstantiated. The adequacy of the ECETOC TRA model was questioned. The references cited do not support an assumption that workers consistently wear appropriate chemical-resistant gloves. It is questionable whether worker training on glove use is routine and adequate. Some workers fail to use gloves even after training. Some scenarios (*e.g.*, soldering) could affect the integrity of gloves. Chemically resistant gloves degrade with age, even over the course of hours, and may not be changed out appropriately. Because improper glove use can make exposures worse (*e.g.*, Rawson et al., 2005), GPFs <1 should be considered at the lower bound. • Recommendations: Consider reducing the assumed GPFs used in the NMP draft risk evaluation, given uncertainty regarding worker training and glove material selection. Provide greater justification for adoption of specific GPF values. Adopt language such as "No unreasonable risk is found if a GPF of X is achieved," leaving room for uncertainty as to whether that outcome can be achieved in practice.	Regarding the numerical values of glove PFs, EPA has not found reasonably available data or methods to improve upon the ECETOC TRA model. Therefore, EPA retains this model and its method and values. In Section 2, EPA has removed assignments/ assumptions of specific glove PFs to apply to each OES. To the extent that scenario-specific information on glove use is available, it is described in Section 2.4.1.2. Table 2-77 has been updated to include worker exposures for all glove PFs for all OESs. EPA agrees that improper glove use can make exposures worse. However, EPA clarified in Section 2.4.1.1 that its approach uses glove PFs to reduce skin surface area. Therefore, using PF < 1 would increase surface area above EPA's assumed values, which is not the likely effect of improper glove use. Also, EPA found no reasonably available approaches or method toward quantifying PF < 1. Improper glove use would create conditions closer to occlusion and would be more likely to increase contact duration as noted in the Supplemental File on Occupational Exposure Assessment. Assuming longer contact durations would be a better approach for improper glove use. For the purpose of this risk evaluation, EPA makes assumptions about potential personal protective equipment (PPE) use based on reasonably available information and expert judgment. EPA considers each condition of use and constructs exposure scenarios with and without engineering controls and /or PPE that may be applicable to particular

		worker tasks on a case-specific basis for a given chemical. Again, while EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected. For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates PPE use based on information underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in Section 5.2. Additionally, in consideration of the uncertainties and variabilities in PPE usage, including the duration of PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determinations in order to address those uncertainties. EPA has also outlined its PPE assumptions in Section 5.1 and EPA's assumptions are described in the unreasonable risk determination for each condition of use, in Section 5.2.
SACC, 54, 56, 57	**SACC COMMENTS:** • Describe how default GPFs are assigned when the type and appropriateness of glove type and proper use or other PPE use are not known. • Use of empirical glove permeability data could strengthen the risk evaluation relative to use of hypothetical GPF. Crook and Simpson (2007) published the results of an NMP glove permeability study that was not cited in the draft risk evaluation. • Committee members questioned the decision to apply the same GPF to all scenarios. Industry-specific protections factors should be considered. • The Committee recommended that EPA lower the assumed GPF to 5 for the following exposure scenarios:	In Chapter 2 and in the Supplemental File on Occupational Exposure Assessment, EPA has removed assignments/ assumptions of specific glove PFs to apply to each OES. Table 2-77 in Section 2.4.1.3 has been updated to include worker exposures for all glove PFs for all OESs. EPA states in Section 2.4.1.1 that, as indicated in Table 2-3, use of PFs above 1 is recommended only for glove materials that have been tested for and shown to be effective for preventing permeation of the NMP-containing liquids associated with the condition of use. Therefore, EPA has included consideration of permeation/ efficacy/ effectiveness by considering use of PFs of 5, 10, and 20.

	Section 2.4.1.2.1 Manufacturing; 2.4.1.2.2 Repackaging; 2.4.1.2.3 Chemical processing, excluding formulation; 2.4.1.2.4 Incorporation into Formulation, mixture or reaction product; and 2.4.1.2.8. Electronic parts manufacturing. • Assumptions underlying assigned GPFs were difficult to follow for individual scenarios, in both the draft risk evaluation and Supplemental File. • Recommendation: State (and display in tabular form) expected glove use and GPF assumed for each condition of use scenario and include an assessment of associated uncertainty. **PUBLIC COMMENTS:** • EPA should incorporate NMP-specific data on glove permeation into its risk assessment to provide a more accurate characterization of their impact on internal dose and risk**.** • EPA was provided with information about the efficacy of different glove materials for reducing potential hazards from NMP-containing paint strippers in a July 2015 report: "Assessment of the Efficacy of Different Glove Materials for Reducing Potential Hazards Associated with NMP Containing Paint Strippers." It was not apparently considered for the draft risk evaluation, nor was it put into the public docket as the Group requested. To ensure that this important information is available and included in the final risk evaluation, the report will soon be published as open access in the Journal of Exposure Science and Environmental Epidemiology.	In Appendix E, EPA presents information gathered in support of understanding glove use for handling pure NMP and for paint and coatings removal using NMP formulations. EPA states in Section 2.4.1.1 that this information in Appendix E may be generally useful for a broader range of uses of NMP and is presented for illustrative purposes. EPA has incorporated NMP-specific data on glove permeation, including information and data from the Crook and Simpson (2007) study, in this appendix. In Section 4.2.2 of the risk evaluation, EPA presents risk estimates for occupational exposures both with and without glove use (glove PFs 1, 5, 10, and 20) for each occupational exposure scenario. Table 4-54 presents risk estimates with and without gloves for all conditions of use.
61	**PUBLIC COMMENTS:** • Notably, "EPA has not found information that would indicate specific activity training (*e.g.*, procedure for glove removal and disposal) for tasks where dermal	EPA includes high-end scenarios with PF = 1 to account for scenarios in which workers are not provided protective gloves, are provided inadequate gloves, or are not adequately trained.

	exposure can be expected to occur in a majority of sites ….” EPA must therefore consider the foreseeable exposure scenarios in which employees are not provided protective gloves, or, worse, are provided inadequate gloves or are not adequately trained and thus face even greater dermal exposures due to glove contamination and occlusion of NMP close to the skin. • EPA assumes that any NMP on the skin is “removed by cleaning at the end of the work period.” EPA offers no evidence that all workers actually do clean their hands and other exposed body parts following each shift, nor that facilities are available for them to do so. In the absence of such cleaning, dermal exposure durations – and associated risks – will be greater than those estimated by EPA. • EPA must consider the fact that clothing can absorb NMP liquids and/or vapors. As many workers return home in the same clothes they were wearing at work, this absorption creates that potential for additional exposures that EPA has not addressed in either of its draft risk evaluations.	EPA has clarified in Section 2.4.1.1 that it is assumed that workers usually clean their exposed skin following each shift. EPA did not find reasonably available information on prevalence of or facilities for cleaning or that dermal contact with liquids will exceed EPA estimates. The frequency and magnitude of take-home exposure is dependent on several factors, including personal hygiene and visibility of the chemical on skin or clothing. EPA does not have methods to reliably predict take-home exposures associated with returning home from work in potentially contaminated clothing.
Dermal exposure - Vapor-through-skin		
SACC	**SACC COMMENTS:** • Discussion of dermal exposures via NMP vapor that penetrates clothing fabrics, and direct skin contact with clothing saturated with NMP vapor, along with associated uncertainties, should be included in the evaluation.	EPA has included discussion in Uncertainties Sections 2.4.1.4 and 4.3 that dermal exposures to NMP vapor that may penetrate clothing fabrics and the potential for associated direct skin contact with clothing saturated with NMP vapor are not included in quantifying exposures. The discussion further notes that these uncertainties could potentially result in underestimates of exposures.
33, 57	**PUBLIC COMMENTS:** • With respect to the dermal vapor pathway, there is clear evidence that this pathway is important in humans since the combined contributions from inhalation and dermal	EPA has included the dermal vapor pathway, which EPA refers to as the vapor-through-skin route. The PBPK model accounts for inhalation exposure, dermal exposure to liquid, and dermal exposure to vapor. EPA discusses vapor-through-

	absorption of vapor (when wearing trousers and short-sleeved shirts) to the internal dose were 1.5- to 1.7-fold higher than that from inhalation alone (Bader et al., 2008). • A fuller characterization of exposure pathways should be conducted for whole-body exposures to humans (*i.e.*, dermal exposure to NMP vapor is explicitly included).	skin exposure in Sections 2.4.1, 3.2.2, and 3.2.5.5 of the risk evaluation. EPA includes discussion of Bader et al. (2008) in Section 3.2.5.5. EPA considers the current characterization of pathways to be clear and adequate.
54, 56	**PUBLIC COMMENTS:** • For the vapor-through-skin route of exposure, EPA assumed that workers wore short-sleeved shirts and long pants. EPA assumed that the head, arms, and hands are entirely exposed unless PPE is worn. Together, the fractional skin area exposed to vapor (SAVC) is 25% of the total skin surface area in the absence of PPE or liquid dermal contact (lines 4774-4781). Information submitted to EPA shows that the practice in industrial settings, such as electronic part manufacturing, is for complete coverage of head, torso, legs, arms, and hands. Assumptions regarding skin exposure for the vapor-through-skin route of exposure should reflect actual industry practice in the use of PPE.	The PBPK model accounts for reduction in skin surface area for vapor-through-skin exposure based on PPE usage. EPA included additional PBPK runs for semiconductor fab workers assuming 98% skin coverage to supplement runs that assume 75% skin coverage. EPA has included discussion in Uncertainties Sections 2.4.1.4 and 4.3 that dermal exposures to NMP vapor that may penetrate clothing fabrics and the potential for associated direct skin contact with clothing saturated with NMP vapor are not included in quantifying exposures. The discussion further notes that these uncertainties could potentially result in underestimates of exposures.
Inhalation exposure		
SACC	**SACC COMMENTS:** • In the draft risk evaluation, three pathways (vapor inhalation, dermal absorption from liquid, and dermal absorption from vapor) were assessed. One Committee member suggested that aerosol inhalation should be investigated as well.	EPA modeled exposures to NMP in aerosols in the commercial automotive servicing OES. Also, EPA states in Section 2.4.1 that inhaled vapor/mist/dust will not be considered as an inhalation exposure because EPA does not have reasonably available data or methods to fractionate the total NMP inhaled into the amount of NMP that deposits in the upper respiratory system and the amount of NMP that enters the lung. EPA considers aerosol to be essentially equivalent to mist.
SACC	**SACC COMMENTS:**	EPA has added to 2.4.1.1 that EPA has modeled inhalation air concentrations for workers in 11 of 16 OESs and far-field

	• Provide justification for not exploring a range of available inhalation exposure models for estimating occupational exposures.	inhalation air concentrations for ONUs in 1 of 16 OESs. EPA has exhausted all modeling opportunities with the data that are reasonably available and therefore was unable to model inhalation air concentrations for workers in the remaining 5 OESs and far-field inhalation air concentrations for ONUs in the remaining 15 OESs.
Aggregate exposure		
SACC	**SACC COMMENTS:** • Recommendation: Estimate aggregate exposures, since some occupational workers may have both dermal and inhalation exposures that are non-negligible, and discuss the relative contributions of each exposure pathway to total exposures.	PBPK modeling for workers estimates aggregate exposure and accounts for dermal, inhalation, and vapor-through-skin routes. In Section 2.4.1.1, EPA added discussion that the relative contributions of each exposure pathway to total exposures varies according to parameter values for NMP weight fraction in the liquid product contacted, skin surface areas in contact with the liquid product and with vapor, durations of dermal contact with liquid product and with vapor, air concentration for inhalation and vapor-through-skin exposure, body weight of the exposed person, and glove protection factor and respirator assigned protection factor (if applicable). In scenarios where the three parameters involving dermal contact with liquid product (NMP weight fraction in the liquid product contacted, skin surface areas in contact with the liquid product and with vapor, durations of dermal contact with liquid product) have relatively high values, this route can be the dominant route for worker exposures.
Exposure monitoring data		
51, 34, 49, 61	**PUBLIC COMMENTS:** • EPA acknowledged it "only found inhalation monitoring data for the use of NMP in semiconductor manufacturing" and had no data at all regarding the use of NMP in manufacturing lithium ion batteries (NMP Risk Evaluation, p. 100) or any “inhalation monitoring data specifically related to the use of NMP-based	EPA revised the occupational exposure assessment in the risk evaluation to separately assess occupational exposure scenarios associated with three categories of electronic part manufacturing: lithium ion battery manufacturing (2.4.1.2.15); Other electronics manufacturing, including capacitor, resistor, coil, transformer, and other inductor manufacturing (2.4.1.2.9); and semiconductor manufacturing

	soldering products." EPA cannot validly make an "unreasonable risk" determination about the use of NMP in lithium ion battery manufacturing, given the Agency's very limited knowledge about how NMP is used in lithium ion batteries and the substantial differences between lithium ion battery manufacturing and semiconductor manufacturing. With regard to soldering, EPA assumed, without any supporting data, that "most NMP may be destroyed in the soldering process, mitigating the potential for significant inhalation exposures."	(2.4.1.2.10). In these separate OESs, EPA revised and expanded PBPK runs for industry-specific work activities using industry-specific air concentration data sets provided in public comments for the lithium ion battery manufacturing industry, for the semiconductor manufacturing industry, and from the OSHA data set for capacitor, resistor, coil, transformer, and other inductor manufacturing (LICM, 2020a; Semiconductor Industry Association, 2020, 2019b, c; OSHA, 2017). EPA revised the Soldering OES in Section 2.4.1.2.12 of the risk evaluation to assess potential inhalation and vapor-through-skin exposures to NMP during soldering by including air monitoring data form a surrogate activity.
Conditions of use – Formulating		
50	**PUBLIC COMMENTS:** • Fujifilm Holdings America Corporation submitted worker exposure data, including air monitoring and manufacturing/handling data on NMP (see below) and requested that EPA consider that, under these existing industrial user conditions, risk to the worker has been minimized, and therefore, handling and use of NMP does not present an unreasonable risk and does not warrant use restrictions that would prevent these successful operations from continuing. • Fujifilm is regulated by multiple federal, state, and local agencies for compliance with both worker and environmental safety. In addition, Fujifilm utilizes Best Management Practices, including PPE as needed to protect the operator against exposure via dermal, oral, or respiratory routes as a required practice. Mandatory worker protection has long been in place and the wearing	EPA revised the air concentration inputs in the Formulation OES in Section 2.4.1.2.4 to incorporate these data provided by Fujifilm (2020). EPA revised the worker activities Section 2.4.2 of the Supplemental File on Occupational Exposure Assessment to include information from Fujifilm that their workers are required to have chemical hygiene training prior to handling NMP. EPA also included additional PPE and engineering control information from Fujifilm in this same section of this supplemental file.

	thereof is a condition of employment when handling such chemicals. ○ No employee is permitted to handle or be exposed to these chemicals before adequate chemical hygiene training. ○ In addition, training and rigorous adherence to the procedures is required at all times. ○ Fujifilm requires the use of long-sleeve rubber gloves, which are impervious to the chemicals. This means that there is no transmittance of any chemical through the gloves to the skin. ○ For further protection, the purpose of the extended glove length is for incidental contact protection. Note: for reference, the gloves in use are Showa brand #3416: neoprene-coated, 15-mil thickness, and 14-inch gauntlet cuff with interlock knit lining. ○ The manufacturing and use of products that contain NMP does not pose an unreasonable risk – inhalation hazards are minimal due to the chemical's low vapor pressure (0.29-0.32 mm/Hg @ 68F) and it is not processed at elevated temperatures. ○ In addition, for skin and eye exposure, employees do not have direct contact with the chemical when processing and packaging. ○ In the case of liquid splashing or spilling, skin and eye exposure and contact is prevented by the required use of safety glasses and impermeable nitrile gloves. Shower rooms and uniform changes are available if needed. ○ Respirator use will vary from operation to operation dependent upon the type ventilation systems the customers have employed. The laminating clears and adhesives are used primarily for credit card	

	production industry and NMP would not be present in the end product. • For open process batch blending: Maximum batch size of 300 gallons containing a concentration of approximately 10-25% NMP. Annual usage is approximately 21,000 lbs. During this process: o PPE: Single use impervious nitrile gloves and safety glasses to prevent dermal exposure. o Ventilation: Facility uses localized ventilation to minimize inhalation exposure. o Industrial hygiene monitoring (air sampling): Because of the chemical's low vapor pressure/volatility and the localized ventilation employed, air monitoring has not been necessary as we do not anticipate detectable amounts. This is additionally based on data from testing at another Fujifilm facility – Carrollton, Texas. Occupational Safety and Health Administration (OSHA) permissible exposure limits (PELs)/time-weighted average (TWA)/short term exposure limits (STELs) are not established for NMP. o Suppliers: Supplied by U.S.-based vendors in 55-gallon drums as 100% NMP or in a resin mixture. o Waste disposal: Waste residue from cleaning equipment and off-specification product is disposed of at a licensed treatment, storage, and disposal facility where it is used as a fuel supplement for energy recovery.	
Conditions of use – Soldering		
34, 61	**PUBLIC COMMENTS:** • EPA proposes a finding that an estimated 4 million workers exposed to NMP from soldering face no unreasonable risks. This finding, based largely on the	EPA revised the Soldering OES in Section 2.4.1.2.12 of the risk evaluation to assess potential inhalation and vapor-through-skin exposures to NMP during soldering by including air monitoring data from a surrogate activity.

	erroneous assumption that all of those workers would have access to and use PPE, is unwarranted.	For the purpose of this risk evaluation, EPA makes assumptions about potential PPE use based on reasonably available information and expert judgment. EPA considers each condition of use and constructs exposure scenarios with and without engineering controls and /or PPE that may be applicable to particular worker tasks on a case-specific basis for a given chemical. Again, while EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected. For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on information and judgment underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in Section 5.2. Additionally, in consideration of the uncertainties and variabilities in PPE usage, including the duration of PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determinations in order to address those uncertainties. EPA has also outlined its PPE assumptions in Section 5.1 and EPA's assumptions are described in the unreasonable risk determination for each condition of use, in Section 5.2
Conditions of use – Lithium ion battery industry		
49, 56	**PUBLIC COMMENTS:** • EPA grouped lithium ion battery manufacturing and lithium ion cell production under the much broader category of "Use in Electronic Equipment, Appliance, and Component Manufacturing," which includes the use of NMP for "cleaning of electronic parts, coating of	EPA revised the occupational exposure assessment in the risk evaluation to separately assess occupational exposure scenarios associated with three categories of electronic part manufacturing: lithium ion battery manufacturing (2.4.1.2.15); Other electronics manufacturing, including capacitor, resistor, coil, transformer, and other inductor

	electronic parts, including magnet wire coatings, and photoresist and solder mask stripping," in addition to "lithium ion battery manufacturing." In so doing, EPA has incorrectly assumed that exposure, engineering and workplace controls, job descriptions, and uses of NMP are substantially similar in all types of manufacturing in this category. In fact, there are few similarities between the use of NMP in manufacturing lithium ion batteries and the other uses of NMP covered by this category (see details below). EPA evaluated little, if any, information about the specific use of NMP in the manufacturing of lithium ion batteries. The exposure scenarios in the draft risk evaluation are based solely on information that EPA gathered about semiconductor manufacturing, which are not applicable to lithium ion battery manufacturing. • EPA cannot validly apply generic exposure assumptions and make an "unreasonable risk" determination about the use of NMP in "lithium ion battery manufacturing," given the Agency's very limited knowledge about, and understanding of, how NMP is used in lithium ion batteries and the substantial differences between potential exposure scenarios in lithium ion battery manufacturing and semiconductor manufacturing. Lithium ion battery manufacturing should be considered as a separate condition of use. • EaglePicher disagrees with EPA's determination that the use of NMP in manufacturing lithium ion batteries presents an unreasonable risk of injury to workers. EPA's assessment must include consideration of engineering controls (described below). If risks are preliminarily identified, EPA then must consider whether the risk is mitigated by the use of PPE, and if so, no finding of unreasonable risk is warranted.	manufacturing (2.4.1.2.9); and semiconductor manufacturing (2.4.1.2.10). In these separate OESs and where feasible, EPA revised and expanded PBPK runs for industry-specific work activities using some industry-specific PBPK input data and information provided in public comments for the lithium ion battery manufacturing industry (EaglePicher Technologies, 2020a, b; LICM, 2020a, b, c) and for the semiconductor manufacturing industry (Intel Corporation, 2020; Semiconductor Industry Association, 2020; Intel Corporation, 2019; Semiconductor Industry Association, 2019a, b, c). EPA's risk conclusions take PPE use into account. In risk characterization, EPA calculated risks for each occupational worker COU with and without various levels of PPE protection. The tables in Section 4 show the extent to which protective gloves and masks mitigate risks.

49, 56	**PUBLIC COMMENTS:**
	• The semiconductor-related NMP activities described above as the basis of EPA's risk assumption are very different from those occurring in the lithium ion cell/battery industry.
	  ○ This industry does not engage in the unloading of trucks containing virgin NMP; it only receives sealed containers of virgin NMP and pre-mixed binder-NMP solution, with no associated exposure risks.
	  ○ This industry does not load trucks with waste NMP, thus eliminating any related risks, or use NMP for "coating of electronic parts or "stripping" of any kind.
	  ○ At no time do any employees come into direct dermal contact with NMP, and the duration of contact is considerably less.
	  ▪ The handling of NMP in small containers in cell manufacturing facilities is limited to infrequent use in the laboratory or small-scale operations where they are opened only in ventilated hood areas with personnel equipped with extensive PPE (*e.g.*, Figure 8) for no more than 30 minutes a shift (even in these operations, mixing and further processing takes place in fully enclosed systems).
	  ○ Employees wear PPE with an assigned protection factor of 1,000 that precludes inhalation or dermal contact.
	  ○ The total volume of NMP used by EaglePicher Technologies, LLC, is small. Their Joplin facility uses <1,100 kg annually. At the East Greenwich facility, the annual volume is only 800 kg.
		EPA assessed lithium ion cell manufacturing work activities indicated by the information in public comments (EaglePicher Technologies, 2020b; LICM, 2020a, b). These activities include: Container handling, small containers; Container handling, drums; Cathode coating; Cathode mixing; Research and development; and, Miscellaneous.
		
		To supplement shift-based contact duration estimates, EPA used the task duration estimates in the public comments to assess what-if (task duration-based) PBPK runs for the lithium ion cell manufacturing.
		
		EPA included summaries of relevant details provided in the public comments, particularly process description and PPE information specific to the lithium ion cell manufacturing industry, in Section 2.15 (Electronics Part Manufacturing OES) of the Supplemental Information on Occupational Exposure Assessment document.
		
		EPA thanks the commenter for providing information on the EPA-issued consent order and Significant New Use Rule (SNUR) for the use of cathode powders and cathode mixing in lithium ion cell manufacturing. These consent orders and SNURs were issued for chemicals that are not NMP.

	• Lithium ion cells are produced in a tightly controlled manufacturing environment and closed pipe systems are used for NMP transfer.
	  ○ The engineering controls and PPE the industry employs are expressly designed to prevent worker exposure to NMP.
	  ▪ Because of purity concerns alone, nowhere in a commercial lithium ion cell manufacturing process are workers expected to immerse their hands in NMP or NMP-based slurries – with or without proper PPE. Non-routine operations such as maintenance activities or recovery from process upsets require the use of PPE because, in the absence of PPE, they could put workers in contact with NMP outside of established engineering controls.
	  ▪ Access to cathode mixing, coating, and drying areas where NMP is used is tightly controlled.
	  ○ Personnel working in mixing and coating areas receive extensive training regarding the processes and proper PPE. Standard Operating Procedures (SOPs) are utilized for routine and non-routine tasks and specify training and required PPE. Personnel entering these areas for routine work must undergo a gowning procedure for quality and safety purposes that includes donning in-process safety shoes, Tyvek suits, nitrile gloves, safety glasses, hairnet, and mask. These PPE are not intended for operations involving intentional contact with NMP or NMP-based slurries.
	  ○ Additional PPE is provided for work that will involve contact or potential contact with NMP and includes chemical resistant suits, respirators, and chemical-resistant gloves, depending on the task performed.	

	These workers are required to wear full-body chemical resistant suits with booties/shoe covers. The equipment includes a PAPR and hood with organic/acid gas + high-efficiency particulate air cartridge coverage. Gloves are required, typically double latex for limited contact with NMP. Butyl gloves are required when contact with NMP is expected. ○ For the purposes of ensuring worker health and safety, exposure risk assessments are conducted to verify the efficacy of engineering and administrative controls. ○ In all cases, lithium ion cell manufacturers strive to control every material in the NMP pathway, including the metals and other materials used in piping, valves, and mixing and coating equipment. Any contact with workers and their PPE is avoided whenever possible. ○ NMP recovery systems are fully automated, closed systems. Only maintenance workers with prescribed PPE interact with these systems. Maintenance procedures are conducted only on de-pressurized systems. This means for large operations, shipments of virgin NMP are less frequent compared to smaller production facilities and other industries. Where these shipments occur, and in the case of condensed NMP liquid shipments and shipments for disposal of degraded NMP and distillation bottoms, workers are fully protected from potential inhalation and dermal exposures through the use of PPE. • Finally, EPA has issued several consent orders and associated significant new use rules for the use of cathode powders that already require the extensive use of	

	PPE in cathode mixing operations during lithium ion cell manufacturing, such as 40 CFR § 721.11027. Therefore, EPA-imposed PPE is already required and should be taken into consideration in this risk evaluation.	
Conditions of use – Magnet wire industrial processing		
47	**PUBLIC COMMENTS:** • The magnet wire industry has long utilized NMP as a solvent/ diluent in high-performance magnet wire enamels, thinners, and cleaners. In the magnet wire industrial process, a copper or aluminum wire is routed through an applicator of solvent-based enamel coating. The size of applicator may vary throughout the industry, but most contain ½-1 gallon of coating, which contains, at most, 80-85% concentration of NMP. NMP does not react with the other ingredients in this coating but is simply mixed in to facilitate the smooth application of the enamel. NMP's role here is critical since rough application of the enamel would result in a blistered film and ultimately cause failure of the magnet wire to create the electro-magnetic field. After leaving the applicator, the wet-coated wire passes through a curing oven where the NMP evaporates from the mixture, leaving a thin film of cured polymer on the wire. Magnet wire usually gets several coats of enamel, each followed by a pass through the curing oven. Once finished, there is no NMP exposure risk to the end-user of which the National Electrical Manufacturers Association (NEMA) is aware under normal conditions of use. o The applicator used for solvent-based enamel coating contains, at most, an 80-85% concentration of NMP. o The curing process occurs in ovens that are completely enclosed, and there is no human exposure to NMP during this process.	EPA updated the process description information and PPE information for the magnet wire coating process in Section 2.9 (Other Electronics Manufacturing OES) of the Supplemental Information on Occupational Exposure Assessment document. As described in Section 1.4.2 of the risk evaluation, EPA did not evaluate exposures via the drinking water pathway or NMP land releases to underground injection, RCRA Subtitle C hazardous waste landfills, or RCRA Subtitle D municipal solid waste (MSW) landfills in this risk evaluation. These exposure pathways fall under the jurisdiction of other EPA-administered statutes and associated regulatory programs. During problem formulation, EPA performed a first-tier screening analysis of risks from ambient air, ambient water, sediment, and land-applied biosolids. EPA did not identify risks from human or environmental exposures that may result from these pathways, including inhalation of outdoor air containing NMP released from industrial and commercial facilities.

	○ Any vapor emitted during application moves directly into the curing oven, wherein at least 90% of the NMP combusts. ○ The finished product contains only trace amounts of NMP due to the curing process previously described. • Another facet to magnet wire manufacturing is maintenance cleaning. Due to regular, widespread industry application of preventive safety measures (described below), use of NMP as a solvent for cleaning/degreasing operations in magnet wire facilities DOES NOT present an 'unreasonable risk' to workers under these conditions of use, as per TSCA Section 6(b)(4)(A). ○ Enameling equipment is bathed in agitated tanks of NMP. These tanks range in size but are commonly around 50 gallons. ○ This process is completely enclosed while equipment is cleaned. When the cycle completes, the operator retrieves the equipment by opening the tank lid, which prompts the basket to rise up and drains the NMP back into the tank. ○ Emissions consist of evaporation from the NMP bath and from the cleaned parts removed from the bath. ○ Human exposure to NMP is controlled through the use of PPE such as gloves, aprons, and goggles, as well as engineering controls. • NMP losses to the environment are limited by strict controls on air emissions through the combustion process mentioned prior. To be sure, some NMP vapors may be emitted, for example, during equipment cleaning. EPA has estimated annual emissions from a magnet wire operating line without an incinerator at 84 Mg/year. Almost all operating lines now have an incinerator, so	

	the actual amount is expected to be much less. • Any liquid waste NMP and/or solid waste wet with NMP (paper, plastic, rags, etc.) are handled in compliance with the Resource Conservation and Recovery Act (RCRA). In the event that small amounts of NMP do leak into the environment, EPA recognized that NMP has low hazard for ecological receptors and low persistence if released into aquatic or terrestrial environments.	
Conditions of use – Semiconductor industry		
52, 64, 31	**PUBLIC COMMENTS:** • NMP is used in semiconductor manufacturing as a solvent or to remove residue from product wafers. Semiconductor manufacturing involves the fabrication of circuits that are typically <100 nanometers in dimension. The process of manufacturing advanced semiconductors takes place in highly advanced and complex fabrication plants ("fabs") and requires exceptionally precise and controlled manufacturing equipment and processes. Such processes occur within equipment, which is, by design, intended to isolate the manufacturing process and chemicals from workers. Modern semiconductor manufacturing tools are enclosed, ventilated, and automated, thus preventing worker exposure. Under these near pristine and highly controlled conditions, there are no unreasonable risks to workers attributable to exposures to NMP. • SIA has provided extensive information to EPA on the industry's practices and procedures for handling NMP, including meeting with EPA officials in November 2017 to summarize the conditions of use of NMP at semiconductor fabs and hosting a group of EPA officials in February 2019 to tour a semiconductor fab of a member company to provide a first-hand understanding	EPA updated the process description and PPE information for semiconductor manufacturing in Section 2.10 (Semiconductor Manufacturing OES) of the Supplemental Information on Occupational Exposure Assessment document. To supplement shift-based contact duration estimates, EPA updated the what-if (task duration-based) work activities for semiconductor manufacturing based on the task duration estimates provided by SIA in public comments (Semiconductor Industry Association, 2020, 2019a). EPA updated the central tendency and high-end NMP weight fractions for the semiconductor work activities using values provided by the SIA in these public comments. EPA added several PBPK runs for semiconductor fab workers assuming 98% skin coverage to supplement runs that assume 75% skin coverage. These runs are available in the Supplemental Excel File on Occupational Risk Calculations. For any particular male Fab worker or Fab ONU activity, the differences in AUC internal concentrations obtained by varying only the assumed whole-body skin coverage between 75% and 98% but no other parameter variation was found to be less than 1% in EPA's anecdotal comparison. Therefore,

	of the use and handling of chemicals at a fab. SIA submitted details on task durations and frequencies, which showed that task durations are short and human exposures are accordingly time-limited. SIA has described its engineering controls and chemical handling procedures to EPA in presentations and in written documentation submitted to EPA. These procedures are designed explicitly to prevent any dermal contact with liquid NMP or other potential forms of residual NMP. Several submissions to EPA describe the risk management measures implemented at fabs, including depictions and descriptions of PPE worn by workers to minimize the potential that they might come in contact with NMP (*e.g.*, specific documented procedures for selecting the proper gloves for a particular chemical and task and for donning and removing the gloves), as well as information concerning the structure and operations of fab facilities, which are designed to largely eliminate opportunities for any human contact with wafers and the chemicals used within semiconductor manufacturing equipment. This information clearly demonstrates that fab workers have minimal opportunities for direct exposures to NMP. • Workplace practices at Intel (listed below), and those that are common in the semiconductor industry, successfully mitigate the risk of worker exposures to NMP. ○ Intel requires work controls, such as flushing filters prior to filter changes, draining of NMP-containing sinks, use of tools to retrieve parts, and use of wipes in addition to chemical-resistant gloves, to minimize contact with NMP during maintenance.	the skin coverage assumption does not appear to significantly impact the AUC internal concentration estimates.

	○ Container changeouts are performed in a dedicated bulk chemical room and dip tubes are utilized for easy container changes. Minimal chemical is exposed during the dip tube change process (potential for a few drops cleaned with a wipe). ○ Employees who perform work in areas or during tasks where they may be exposed to NMP are required to use chemical resistant PPE. The current PPE required includes MAPA Trionic 514+ (or equivalent) chemical-resistant gloves, chemical resistant gowns, and eye and face protection. PPE assessments are performed and documented by Intel's Environmental Health & Safety professionals prior to use of NMP. ○ In addition, semiconductor fab workers wear long-sleeved coveralls with hoods and boots as well as gloves and safety glasses that provide ≥98% skin coverage. PPE such as chemical-resistant aprons and gloves, face shields, and respiratory protection are used when necessary to further reduce worker exposure. Clothing and PPE provide ≥96% skin coverage for workers performing NMP-related tasks outside the fab. ○ Employees working with NMP are required to take documented safety training to ensure that they are qualified to perform tasks and can don and doff and dispose of PPE safely. In addition to the PPE training, equipment-specific training and chemical safety training is required for employees who work with NMP and/or in areas where NMP is used. ○ Intel uses multiple engineering and administrative controls to successfully reduce the risk of exposure to NMP and other chemicals in the workplace.	

	Engineering controls include the use of bulk chemical delivery to reduce manual handling of chemical containers, lockout/tagout to turn off bulk chemical supplies prior to equipment maintenance, flushing of filters and housing prior to work, integrated local ventilation exhaust on manufacturing equipment, liquid leak detection systems, use of ventilated parts clean sinks or hoods for parts cleaning, and emergency machine off systems. Administrative controls include the use of tools, parts clean baskets, and wipes to handle any chemical or chemical-contaminated parts in order to reduce contact with chemicals (chemical-resistant PPE is still required), immediate bagging of contaminated parts and waste, and a prohibition on immersion of gloves in liquid chemicals.	
52, 31, 64	**PUBLIC COMMENTS:** • Monitoring data (described below) submitted by SIA to EPA confirm that worker exposure at semiconductor fabs is minimal and presents no unreasonable risks to human health. SIA submitted contemporary information on worker exposure at semiconductor fabs collected by member companies (see SIA's 2019 workplace exposure study at Appendix A). These data included 118 air sampling datasets and details regarding the durations and frequencies of tasks undertaken by workers in fab facilities. o Only 5 of the 118 personal air samples that SIA member companies collected showed concentrations of NMP above the limits of detection (LODs). Three of the five samples (0.01, 0.02, and 0.07 ppm) were for fab maintenance tasks. Two of the five were for waste truck load/virgin NMP truck offload – tasks	EPA updated the air concentrations for semiconductor manufacturing work activities and did not adjust the duration-adjusted air concentrations to normalize to contact duration estimates due to the high number of non-detect values. The air concentration values used by EPA are very similar to those proposed by SIA in the public comment (Semiconductor Industry Association, 2020) with their proposed input values for PBPK runs. Frequency of truck unloading is accounted for in the analysis by modeling only acute and not chronic exposures for this work activity.

	that occur at many industrial sites and that are not specific to semiconductor manufacturing where measured exposures were <0.4 and 1.2 ppm. ○ Of the 5 measured samples that did have NMP concentrations above LOD, the highest 8-hour TWA concentration was 1.18 ppm for tanker truck offloading. The virgin NMP truck offload task is conducted once per year and corrective actions have been identified to reduce potential exposures. The measured exposure in this instance was only 0.18 ppm above the Cal/OSHA 1.0 ppm 8-hour TWA, more than a factor of 3 less than the 3.5 ppm ECHA limit, and 10 times lower than AIHA's 10 ppm 8-hour Workplace Environmental Exposure Limit. • Intel began exposure sampling in the 1990's to evaluate and address potential workplace exposures to NMP. As no OSHA federal PEL exists, Intel adopted the CAL OSHA limit of 1 ppm (8-hour TWA) in 2006. Because Intel employees work 12-hour shifts, Intel employs a reduced exposure limit of 0.76 ppm (extrapolated from CAL OSHA's 8-hour PEL of 1 ppm). In 2018, with risk assessments being performed in Europe by the ECHA for purposes of Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) and in the United States under TSCA, Intel conducted another thorough review of employee use and exposure to NMP. In its 2018 updated analysis, Intel collected data from its large manufacturing sites in the United States, Ireland, and Israel. The 2018 data were provided to EPA as a subset of the observations reported in the submission made by the SIA. ○ All 2018 breathing zone samples collected at Intel were orders of magnitude below the CAL OSHA	

	exposure limit, and 43 out of the 44 samples collected were below the detection limit for the validated National Institute for Occupational Safety and Health (NIOSH)/OSHA methods (analyses were performed using either NIOSH 1302 or OSHA PV2043 SOP-5, with method detection limits of 3 or 5 µg, respectively). ○ The analysis included all job categories where employees could potentially be exposed to NMP and included the following: equipment maintenance (working on equipment that contains NMP where there is potential for contact with NMP), routine operations (working in the vicinity of NMP but no physical contact with NMP), and container changeouts (changing bulk NMP containers). Statistical analysis of the 2018 and past data using the AIHA IHSTAT statistical modeling package indicated a very low probability of exceeding Intel's adopted exposure limit of 1 ppm (*i.e.*, at a 95% confidence level, the likelihood of exceeding the CAL OSHA OEL is $3.4x10^{-8}$).	
52, 31, 64	**PUBLIC COMMENTS:** • In the draft risk evaluation, semiconductor manufacturing was inappropriately grouped with "Paint additives and coating additives not described by other codes" (p. 315) and "Solvents (for cleaning or degreasing): Use in electrical equipment, appliance and component manufacturing" (p. 316-317). The semiconductor industry should be assessed separately, rather than as part of a broader "electronics parts manufacturing" sector. • The semiconductor manufacturing is considerably different from these other industrial operations. EPA's	EPA revised the occupational exposure assessment in the risk evaluation to separately assess occupational exposure scenarios associated with three categories of electronic part manufacturing: Lithium ion battery manufacturing (2.4.1.2.15); Other electronics manufacturing, including capacitor, resistor, coil, transformer, and other inductor manufacturing (2.4.1.2.9); and Semiconductor manufacturing (2.4.1.2.10). In these separate OESs and where feasible, EPA used some industry-specific PBPK input data and information provided in public comments for the lithium ion battery manufacturing industry (EaglePicher Technologies, 2020a, b; LICM, 2020a, b, c) and for the semiconductor manufacturing

	draft risk evaluation improperly grouped semiconductor manufacturing along with other industrial activities that have differing conditions of use. EPA's assumption that the practices in the semiconductor manufacturing industry are similar to other electronics manufacturing operations is not accurate and is inconsistent with the Agency's risk evaluation rules. The regulations at 40 CFR 702.41(a)(5) require that risk evaluations rely on analyses that are "suited for their intended purpose" and "well-tailored" to enable a "technically sound determination" concerning the conditions of use. In evaluating the conditions of use in semiconductor operations within the same category as other industry sectors with different operations and conditions of use, EPA relied on estimates of dermal exposures that greatly exaggerated the conditions documented in the exposure study SIA provided to EPA and incorrectly applied the same assumptions and drew the same conclusions for all conditions of use in this broad range of categories. • It is inappropriate and unnecessary to group the semiconductor industry's conditions of use of NMP with other industrial sectors when EPA had available the information needed to better understand and more reasonably evaluate the potential for semiconductor workers to be exposed to NMP under the conditions of use unique to semiconductor fabrication facilities. Unfortunately, it appears that much of the information and data that SIA provided were not incorporated in the draft risk evaluation docket and may not have been thoroughly reviewed or were only partially considered by EPA personnel when preparing the draft risk evaluation. This reflects a deficiency that should be corrected before the final risk evaluation is prepared and this must be	industry (Intel Corporation, 2020; Semiconductor Industry Association, 2020; Intel Corporation, 2019; Semiconductor Industry Association, 2019a, b, c). EPA reviewed all information in the public comments provided by SIA and updated the PBPK inputs for the semiconductor manufacturing OES work activities, including NMP weight fractions, NMP air concentration, and task duration (for what-if, task duration-based work activities). In Chapter 2, EPA has removed assignments/ assumptions of specific glove PFs to apply to each OES. Table 2-77 has been updated to include worker exposures for all glove PFs for all OESs. Table 2-77 in Section 2.4.1.3 has been updated to include worker exposures for all glove PFs for all OESs. EPA clarified in Section 2.4.1.1 that EPA has no reasonably available information on actual surface area of contact with liquid and that the assumed values represent adequate surrogates for most uses' central tendency and high-end surface areas of contact with liquid that may sometimes include exposures to much of the hands and also beyond the hands, such as wrists, forearms, neck, or other parts of the body. EPA accounts for distributed values using the central tendency and high-end assumptions for surface areas. EPA clarified in Section 2.4 that non-immersive dermal contact with liquid films is evaluated.

	accomplished if the Agency is to meet its obligations under Section 26 of the amended statute to consider information that is readily available and apply a weight-of-the-evidence approach when assessing risks. By ignoring or undervaluing the SIA data, EPA failed to rely on the best available information and therefore did not apply a weight-of-the-evidence approach. • Based on the data submitted by SIA, EPA should consider the conditions of use in the semiconductor manufacturing sector separately from those in other industrial activities and sectors. Specifically, EPA should take into account: o Duration and frequency of tasks during which exposures to NMP can occur (*e.g.*, truck unloading), o PPE used during such operations, o Engineering controls employed to minimize exposure, and o Sampling data indicating the extremely low potential exposure to NMP when used in fab operations, which take place in a controlled environment inside manufacturing equipment and in maintenance tasks. • Task descriptions provided by SIA (2019a) show that there are generally limited opportunities for skin contact with NMP-containing liquid based on the work descriptions. If EPA chooses to consider dermal exposure, EPA should use the information provided to reassess and refine its dermal exposure estimates specifically for the conditions of use in semiconductor manufacturing operations. In particular, EPA should: (1) assign the highest level protection factors (PFs) in modeling of the level of dermal protection provided by gloves used in semiconductor manufacturing operations; (2) reduce the estimated duration of potential dermal	

	exposures during semiconductor manufacturing operations to no greater than 2 hours/day per individual; and (3) employ a surface area for dermal exposure that is substantially less than immersion of full hands.	
Conditions of use – Small scale operations		
45	**PUBLIC COMMENTS:** • EPA should consider evaluating small-scale conditions of use separately from the bulk loading from drums and from large-scale laboratory use. Hach manufactures chemical reagents and instruments for water quality analysis. NMP is an ingredient in the Hach product, Silver 2 Reagent Solution Pillows. This laboratory reagent is sold only in unit-dose packaging containing <5 mL solution per test. Exposures are limited by both the small amount handled in the unit-dose package and the required PPE. In this industry, small-scale incorporation of NMP into a mixture occurs, in which NMP is transferred from hand-held containers, such as a 1-gallon container, to the mixing vessel. Fewer than 10 gallons/day of NMP are handled, and workers are required to wear PPE. This is very different than the EPA assumption that workers unload bulk NMP from 20 drums per hour.	EPA updated the process description in Section 2.14 (Laboratory Use OES) of the Supplemental Information on Occupational Exposure Assessment based on this information. For the Laboratory Use OES, EPA did not find reasonably available data to distinguish separate PBPK input parameters based on scale.
Conditions of use – Disposal		
34, 55, 51, 61	**PUBLIC COMMENTS:** • The NMP draft risk evaluation does not assess exposure or evaluate the risks associated with disposal-related releases, including spills and accidents, as it is required to do under TSCA. EPA states that "disposal of NMP via underground injection is not likely to result in environmental and general population exposures" because such injection is regulated under SDWA and RCRA. This is untrue (NMP is not regulated as	As described in Section 1.4.2 of the risk evaluation, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the scope of the risk evaluation for NMP using authorities in TSCA Sections 6(b) and 9(b)(1).

	hazardous waste under RCRA) and in violation of TSCA, which expressly defines disposal as a condition of use, requiring EPA to evaluate risks associated with disposal, as opposed to merely assuming that those risks will be adequately managed under other laws. EPA provides no evidence that exposure and risk are insignificant for NMP releases to underground injection wells and hazardous waste landfills or that existing regulations adequately control these pathways for environmental release. • As noted in the NMP Problem Formulation, "NMP has been detected in industrial landfill leachate (Danish EPA, 2015). Although it is not currently subject to any proposed or promulgated water regulations, NMP has been detected in wastewater (WHO, 2001) and is included on EPA's Drinking Water Contaminant Candidate Lists (CCL) 3 and 4 because it is a suspected contaminant in public water systems that may require regulation under SDWA." EPA has acknowledged that "no [landfill] liner can be expected to remain impervious forever," and that "even with stringent waste management standards, waste management units may fail, accidents may occur during transport and handling, and … chemicals may continue to be released and build up in the environment." EPA must assess the concentrations found in air and water (surface and ground) near injection (and other disposal) facilities. • In the Problem Formulation for NMP, EPA acknowledged that it should identify "Other groups of individuals within the general population who may experience greater exposures due to their proximity to conditions of use identified in Section 2.2 that result in releases to the environment and subsequent exposures	While NMP is not classified as RCRA hazardous waste, RCRA Subtitle C hazardous waste landfills and RCRA Subtitle D municipal solid waste (MSW) landfills where NMP may be disposed are subject to regulation under RCRA. These methods of disposal fall under the jurisdiction of and are addressed by other EPA-administered statutes and associated regulatory programs. Environmental disposal of NMP via injection into Class I wells is covered under the jurisdiction of SDWA and disposal of NMP via underground injection is not likely to result in environmental and general population exposures. NMP is one of 109 contaminants listed on EPA's fourth CCL. Because the drinking water exposure pathway for NMP is being addressed under the regular analytical processes used to identify and evaluate drinking water contaminants of potential regulatory concern for public water systems under SDWA, EPA has not included this pathway in the risk evaluation for NMP under TSCA. As a result, EPA did not evaluate exposures via the drinking water pathway or on-site NMP land releases that go to RCRA Subtitle C hazardous waste landfills or RCRA Subtitle D municipal solid waste (MSW) landfills, or associated exposures to the general population or terrestrial species, in the risk evaluation. The comment recommends identifying fenceline communities as PESS and urges EPA to evaluate risk of cumulative exposures. Populations exposed through pathways excluded from the risk evaluation were not identified as PESS. EPA disagrees with public comments on the draft risk evaluation that suggest fenceline subpopulations should be identified as PESS. TSCA provides EPA with the discretion to identify the PESS that are relevant to the chemical-specific risk evaluation [TSCA Section 6(b)(4)(A)]. General population exposure through air, surface

	(*e.g.*, individuals who live or work near manufacturing, processing, use or disposal sites).” This might include tribal communities, workers, and other members of the public who might spend time on the site, live near the site, and consume food and water from near the site. EPA should identify all populations living near disposal and other waste management sites as potentially exposed subpopulations. The multiple exposure scenarios associated with proximity to unlined disposal site releases to environmental media, including air, water, and waste pathways excluded from the NMP draft risk evaluation, must be analyzed for both individual and cumulative exposures.	water, sediment, and land-applied biosolids were evaluated based on fate properties of NMP and screening level analysis. As described in Section 4.6.1.3, EPA did not identify risks to the general population through these pathways. As described in Section 1.4.2, general population exposures through drinking water and disposal are beyond the scope of the risk evaluation. EPA considered the reasonably available information and used the best available science to determine whether to consider aggregate or sentinel exposures for a particular chemical. EPA evaluated aggregate risks across exposure routes for each condition of use but concluded that there is insufficient information about likely co-exposures to support analysis of aggregate exposure across multiple conditions of use. Spills and leaks generally are not included within the scope of a TSCA risk evaluation because, in general, they are not considered to be circumstances under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of. To the extent there may be potential exposure from spills and leaks, EPA is also declining to evaluate environmental exposure pathways addressed by other EPA-administered statutes and associated regulatory programs. First, EPA does not identify NMP spills or leaks as “conditions of use.” EPA does not consider NMP spills or leaks to constitute circumstances under which NMP is manufactured, processed, distributed, used, or disposed of, within TSCA’s definition of “conditions of use.” Congress specifically listed discrete, routine chemical lifecycle stages within the statutory definition of “conditions of use” and EPA does not believe it is reasonable to interpret “circumstances” under which NMP is manufactured, processed, distributed,

		used, or disposed of to include uncommon and unconfined spills or leaks for purposes of the statutory definition. Further, EPA does not generally consider spills and leaks to constitute "disposal" of a chemical for purposes of identifying a COU in the conduct of a risk evaluation. In addition, even if spills or leaks of NMP could be considered part of the listed lifecycle stages of NMP, EPA has "determined" that spills and leaks are not circumstances under which NMP is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of, as provided by TSCA's definition of "conditions of use," and EPA is therefore exercising its discretionary authority under TSCA Section 3(4) to exclude NMP spills and leaks from the scope of the NMP risk evaluation. The exercise of that authority is informed by EPA's experience in developing scoping documents and risk evaluations, and on various TSCA provisions indicating the intent for EPA to have some discretion on how best to address the demands associated with implementation of the full TSCA risk evaluation process. Specifically, since the publication of the Risk Evaluation Rule, EPA has gained experience by conducting ten risk evaluations and designating forty chemical substances as low- and high-priority substances. These processes have required EPA to determine whether the case-specific facts and the reasonably available information justify identifying a particular activity as a "condition of use." With the experience EPA has gained, it is better situated to discern circumstances that are appropriately considered to be outside the bounds of "circumstances… under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of" and to thereby meaningfully limit circumstances subject to evaluation. Because of the expansive and

		potentially boundless impacts that could result from including spills and leaks as part of the risk evaluation (*e.g.*, due to the unpredictable and irregular scenarios that would need to be accounted for, including variability in volume, frequency, and geographic location of spills and leaks; potential application across multiple exposure routes and pathways affecting myriad ecological and human receptors; and far-reaching analyses that would be needed to support assessments that account for uncertainties but are based on best available science), which could make the conduct of the risk evaluation untenable within the applicable deadlines, spills and leaks are determined not to be circumstances under which NMP is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of, as provided by TSCA's definition of "conditions of use." Exercising the discretion to not identify spills and leaks of NMP as a COU is consistent with the discretion Congress provided in a variety of provisions to manage the challenges presented in implementing TSCA risk evaluation. See *e.g.*, TSCA Sections 3(4), 3(12), 6(b)(4)(D), 6(b)(4)(F). In particular, TSCA Section 6(b)(4)(F)(iv) instructs EPA to factor into TSCA risk evaluations "the likely duration, intensity, frequency, and number of exposures under the conditions of use…," suggesting that activities for which duration, intensity, frequency, and number of exposures cannot be accurately predicted or calculated based on reasonably available information, including spills and leaks, were not intended to be the focus of TSCA risk evaluations. And, as noted in the preamble to the Risk Evaluation Rule, EPA believes that Congress intended there to be some reasonable limitation on TSCA risk evaluations, expressly indicated by the direction in TSCA Section 2(c) to "carry out [TSCA] in a reasonable and prudent manner."

		For these reasons, EPA is exercising this discretion to not consider spills and leaks of NMP to be COUs. Second, even if NMP spills or leaks could be identified as exposures from a COU in some cases, these are generally not forms of exposure that EPA expects to consider in risk evaluation. TSCA Section 6(b)(4)(D) requires EPA, in developing the scope of a risk evaluation, to identify the hazards, exposures, conditions of use, and potentially exposed or susceptible subpopulations the Agency "expects to consider" in a risk evaluation. This language suggests that EPA is not required to consider all conditions of use, hazards, or exposure pathways in risk evaluations. EPA has chosen to tailor the scope of the risk evaluation to exclude spills and leaks in order to focus analytical efforts on those exposures that present the greatest potential for risk. In the problem formulation documents for many of the first 10 chemicals undergoing risk evaluation, EPA applied the same authority and rationale to certain exposure pathways, explaining that "EPA is planning to exercise its discretion under TSCA 6(b)(4)(D) to focus its analytical efforts on exposures that are likely to present the greatest concern and consequently merit a risk evaluation under TSCA...." This approach is informed by the legislative history of the amended TSCA, which supports the Agency's exercise of discretion to focus the risk evaluation on areas that raise the greatest potential for risk. See June 7, 2016 Cong. Rec., S3519-S3520. In addition to TSCA Section 6(b)(4)(D), the Agency also has discretionary authority under the first sentence of TSCA

		Section 9(b)(1) to "coordinate actions taken under [TSCA] with actions taken under other Federal laws administered in whole or in part by the Administrator." TSCA Section 9(b)(1) provides EPA authority to coordinate actions with other EPA offices, including coordination on tailoring the scope of TSCA risk evaluations to focus on areas of greatest concern rather than exposure pathways addressed by other EPA-administered statutes and regulatory programs, which does not involve a risk determination or public interest finding under TSCA Section 9(b)(2). EPA has already tailored the scope of this risk evaluation using such discretionary authorities with respect to exposure pathways covered under the jurisdiction of other EPA-administered statutes and associated regulatory programs (see Section 1.4.3).
34	**PUBLIC COMMENTS:** • NMP is present in bio-solids from wastewater treatment, which are then applied to land as fertilizer. EPA excludes biosolids from the NMP draft risk evaluation because "NMP concentrations in surface water resulting from land application of biosolids are expected to be much less than those associated with direct release of wastewater treatment plant effluents to surface water." EPA offers no support for that statement, and it does not evaluate the combined effects of NMP from direct discharges and biosolids application on the same waterbodies.	As described in Section 2.1.1 of the risk evaluation, EPA considered exposures from biosolids during problem formulation and concluded that no further analysis of this pathway was needed. In the NMP Problem Formulation, EPA explains that "NMP exhibits high water solubility (1000 g/L) and limited potential for adsorption to organic matter (estimated log K_{oc} = 0.9); therefore, land releases will ultimately partition to the aqueous phase (*i.e.*, biosolids associated waste water and soil pore water) upon release into the environment. Because NMP readily biodegrades in environments with active microbial populations, NMP residues that remain following waste water treatment are not expected to persist. NMP concentrations in biosolids-associated water are expected to decrease, primarily via aerobic degradation, during transport, processing (including dewatering), handling, and land application of biosolids (which may include spraying)."

53, 55	**PUBLIC COMMENTS:** • Legacy use of products containing NMP was not considered in this draft risk evaluation. Per decision of the Ninth Circuit Court of Appeals, EPA can no longer exclude "legacy" chemical uses from a risk evaluation, nor can it exclude any conditions of use from consideration. The Court also affirmed that "TSCA's definition of 'conditions of use' clearly includes uses and future disposals of chemicals." EPA does not have the discretion to pick-and-choose conditions of use for inclusion in a risk evaluation.	EPA did not identify any "legacy uses" or "associated disposals" of NMP, as those terms are described in EPA's Risk Evaluation Rule, 82 FR 33726 (July 20, 2017). Therefore, no such uses or disposals were added to the scope of the risk evaluation for NMP following the issuance of the opinion in Safer Chemicals, Healthy Families v. EPA, 943 F.3d 397 (9th Cir. 2019). The uses of NMP in the past are not "legacy" uses. As described in EPA's Risk Evaluation Rule (82 FR 33726 (July 20, 2017)), a legacy use is an ongoing use of a chemical substance in a particular application where the chemical substance is no longer being manufactured, processed, or distributed in commerce for that application. The example provided in the Rule is insulation, which may be present in buildings after a chemical substance component is no longer being made for that use. EPA is not aware of legacy NMP uses.
Conditions of use – Other		
	SACC COMMENTS: • Recommendation: Include NMP as an agrochemical formulant as an occupational use in the draft risk evaluation and discuss implications for exposure and risk. • Only active pesticidal ingredients are regulated under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), not formulants (adjuvants). Therefore, this use does not fall within the purview of any other office of the Agency.	NMP is used as an inert ingredient in pesticide products. Agricultural chemical inert ingredients are considered from a risk perspective. Such agents are often included in pesticide formulations for a number of reasons. EPA understands this use as an ingredient in pesticides would be regulated under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and is therefore outside the definition of chemical substance as regulated by TSCA.
63	**PUBLIC COMMENTS:** • EPA should carefully consider the ways in which conditions of use can vary across different segments of industry, and consider the actual, rather than	EPA appreciates the commenters' suggestion. TSCA (U.S.C. § 3(4)) defines the conditions of use as ''the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or

	hypothetical, conditions of use in specific industry sectors within the scope of the risk evaluation.	disposed of." EPA carefully considered the best approach to describe the conditions of use across and within sectors using NMP, and relied on communications with companies, industry groups, environmental organizations, and public comments to supplement the use information. In the occupational assessment, EPA presents variations across different segments of industry when reasonably available data are found. For example, EPA revised the occupational exposure assessment in the risk evaluation to separately assess occupational exposure scenarios associated with three categories of electronic part manufacturing: lithium ion battery manufacturing (2.4.1.2.15); Other electronics manufacturing, including capacitor, resistor, coil, transformer, and other inductor manufacturing (2.4.1.2.9); and semiconductor manufacturing (2.4.1.2.10). In these separate OESs and where feasible, EPA revised and expanded PBPK runs for industry-specific work activities using industry-specific PBPK input data and information provided in public comments for the lithium ion battery manufacturing industry (EaglePicher Technologies, 2020a, b; LICM, 2020a, b, c) and for the semiconductor manufacturing industry (Intel Corporation, 2020; Semiconductor Industry Association, 2020; Intel Corporation, 2019; Semiconductor Industry Association, 2019a, b, c).
31, 52	**PUBLIC COMMENTS:** • NMP concentrations in specific conditions of use should be considered in the overall risk evaluation. SIA provided data on NMP weight percentage in chemical formulations and waste as part of its 2019 study.	EPA used NMP concentration data specific to the conditions of use being assessed, including weight fractions provided by SIA. Section 2.4.1.1 of the draft risk evaluation details the parameters considered for the PBPK model. To support the draft risk evaluation, EPA determined the weight fraction of NMP in various products through information provided in the available literature, Safety Data Sheets, previous risk assessments and the 2017 NMP Market Profile. Where a data

		point was provided as a range of NMP concentrations for a certain product (*e.g.*, paints and coatings), EPA utilized the mid-range (middle) and high-end (maximum) weight fractions to estimate potential exposures. Where multiple data points for a given type of product (*e.g.*, paints and coatings) were available, EPA estimated exposures using the central tendency (50th percentile) and high-end (95th percentile) NMP concentrations. The SIA-provided weight fraction data were used in the Semiconductor Manufacturing OES in Section 2.4.1.2.10.
31	**PUBLIC COMMENTS:** • On the basis of the draft risk evaluation and the materials made public in the supplemental assessments, SIA reviewers have not been able to reproduce EPA's statistical analysis when interpreting the air sampling results. This lack of transparency makes it difficult for other scientists to fully assess whether EPA is making use of the best available science.	EPA updated the air concentrations for work activities assessed for semiconductor manufacturing. EPA provided additional explanation of the analysis of SIA's air sampling results in the Supplemental Information on Occupational Exposure Assessment.
51	**PUBLIC COMMENTS:** • NMP is not regulated as a Hazardous Air Pollutant (HAP) under the Clean Air Act (CAA) so there are no applicable federal emission limits and no reason to expect that EPA will use the CAA to evaluate the risks of NMP air emissions and take action to reduce this source of exposure.	NMP is not regulated as a hazardous air pollutant. As described in Section 4.6.2.3, EPA performed a first-tier screening analysis for risks from ambient air exposures during problem formulation. EPA did not identify risks from human exposures that may result from inhalation of outdoor air containing NMP released from industrial and commercial facilities.
Exposure for Occupational Non-Users (ONUs)		
SACC	**SACC COMMENTS:** • Very limited data informs ONU exposure assumptions. In particular, the apparent paucity of actual data underlying the ONU air concentration assumption was noted. • Several Committee members expressed concern that the assumption that ONUs were always exposed to cleaner	Table 4-47 shows that EPA found no reasonably available NMP air concentration data for ONUs, including relevant area monitoring. EPA updated Section 2.4.1.1 to indicate that EPA does not have reasonably available parameters, including proximity of ONUs to workers or to emission sources, to estimate near-field/ far-field NMP air concentrations for both workers and ONUs except for the

	(unfiltered) air than users was questionable, given that both near field/far field separation distances and facility air handling equipment were likely to be highly variable both across and within industries. • One Committee member pointed out ONUs in home enterprises might be children in very close proximity to users. • One Committee member felt that ONU and worker exposures were not sufficiently distinguished and/or contrasted. • Recommendation: Develop specific ONU exposure scenarios for each condition of use, and tabulate expected exposures based on the information that has already been collected. • Recommendation: Discuss the potential for modeling ONU air exposures as a function of proximity to active use, including why proximity may be more important for some conditions of use than others.	Commercial Automotive Servicing OES. EPA used this model to estimate near-field/ far-field NMP air concentrations for the Commercial Automotive Servicing OES, as described in the Supplemental Information on Occupational Exposure Assessment. EPA also updated Section 2.4.1.1 to note that proximity may be more important for some conditions of use where ONUs are in close proximity to workers or to emission sources. Also, Section 2.4.1.1 states that "EPA expects that ONUs are exposed to lower air concentrations than workers since they may be further from the emission source than workers," which is similar to the comment (that ONUs were always exposed to cleaner (unfiltered) air compared to workers). EPA agrees that both near field/far field separation distances and facility air handling equipment are likely to be highly variable both across and within industries but has not found reasonably available data that refutes EPA's expectation. ONU modeling is for adults only. Children are covered as bystanders in consumer modeling (see Section 2.4.2.5). In each subsection of 2.4.1.2, EPA describes whether or not ONU-specific monitoring data or modeling is available for each OES. EPA developed specific PBPK runs for ONUs for each OES using NMP air concentration estimates for workers except for the Commercial Automotive Servicing OES that uses estimates of near-field and far-field NMP air concentrations. These PBPK runs are presented in the Supplemental Excel File on Occupational Risk Calculations. Table 2-77 presents the results of the ONU PBPK runs for all OESs.
34, 61	**PUBLIC COMMENTS:** • The range of workers defined by EPA as ONUs – which include "supervisors, managers, engineers, and other personnel in nearby production areas" – is too broad to	EPA has not found additional reasonably available information or data to explore different categories of ONUs beyond the ONU categories presented in this risk evaluation. EPA presents all reasonably available information on the job

	warrant a single categorization. Supervisors and managers have very different exposure patterns than skilled trade workers and other "shop floor" ONUs, yet all of them are assumed to face similar risks under EPA's categorization. Separate ONU worker categories should be considered.	descriptions and functions of ONUs in NMP workplaces in each subsection of 2.4.1.2 and in the Supplemental Information on Occupational Exposure Assessment.
51, 61	**PUBLIC COMMENTS:** • EPA's determination that there are no unreasonable risks to ONUs is unsupportable (pp. 27-28). The draft risk evaluation provides few details on the job functions of ONUs in NMP workplaces, number of ONUs exposed to NMP, and the nature and duration of this exposure. • It is assumed that all ONUs lack dermal contact with NMP, but this assumption is implausible. Cleaning and maintenance of NMP-contaminated equipment would unavoidably result in dermal contact, as would sampling and testing of NMP-containing process streams or products for quality control purposes; spills and equipment leaks would also likely result in dermal contact. ONUs are also less likely to be provided PPE, and therefore, exposure may be as great, or greater than, those of other workers. Removing dermal exposure entirely from EPA's determination of risks to ONUs severely skews EPA's risk estimates and ignores exposure scenarios that are highly likely in real-world use and handling of NMP. • EPA also claims "ONU inhalation exposures are expected to be lower than inhalation exposures for workers directly handling the chemical substance" (p. 303). To account for this assumed difference in inhalation exposure, EPA bases its unreasonable risk determinations for ONUs on "central tendency risk estimates" rather than high-end inhalation exposure	EPA added all reasonably available information on the job functions of ONUs in NMP workplaces in Section 2.4.1.2 subsections. In Table 2-4, EPA presents numbers of ONUs in each OES where exposure to NMP may occur. In Section 2.4.1.1, EPA clarified that the nature and duration of ONU exposure is inhalation and vapor-through-skin and occurs over the same duration, whether based on task or shift duration, as estimated for the worker. EPA considers the activities of cleaning and maintenance of NMP-contaminated equipment, and sampling and testing of NMP-containing process streams or products for quality control purposes, to be worker activities because they may result in dermal contact with liquids. EPA generally defines ONUs in Section 2.4.1 of the RE as "supervisors, managers, and other employees that may be in the production areas but do not perform tasks that result in direct dermal contact with liquids." Based on this definition, EPA does not expect ONUs to have dermal exposures to liquids. Where EPA had monitoring or modeled data specific to ONUs, unreasonable risk determinations were made based on high-end exposures. For conditions of use where the data did not distinguish between worker and OINU inhalation exposures, there was uncertainty regarding ONU exposure.

	levels. Assuming that there is never high-end inhalation exposure by ONUs is unsupportable, since there are undoubtedly some ONU inhalation exposure scenarios that are similar in magnitude and duration to those of workers involved in direct NMP operations. For example, workers in shared work areas close to equipment emitting NMP vapors could have nearly the same level of inhalation exposure as workers using this equipment. The Agency itself acknowledges that, "[w]hen EPA does not have ONU-specific exposure data, EPA's assumption that 50th percentile air concentrations predicted for workers in these activities are a good approximation of exposure is uncertain." • The draft risk evaluation does not include workplace monitoring data to show exposure levels for ONUs specifically. • EPA must obtain more information about real-world ONU exposure scenarios or base its risk determinations on more plausible default assumptions that reflect likely conditions in NMP workplaces.	In each subsection of 2.4.1.2, EPA describes whether or not ONU-specific monitoring data or modeling is available for each OES. EPA does not have reasonably available data or information to develop more plausible default assumptions for ONUs. EPA had sufficient reasonably available information to complete the NMP risk evaluation using a weight of the scientific evidence approach based on the best available science. EPA selected the first 10 chemicals for risk evaluation based in part on its assessment that these chemicals could be assessed without the need for regulatory information collection or development. When preparing this risk evaluation, EPA obtained and considered reasonably available information, defined as information that EPA possesses, or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation. In some cases, when information available to EPA was limited, the Agency relied on models; the use of modeled data is in line with EPA's final Risk Evaluation Rule and EPA's risk assessment guidelines.
Environmental pathways of human exposure		
51, 55, 61	**PUBLIC COMMENTS:** • The NMP draft risk evaluation departs from – in the SACC's words – basic "risk assessment principles" by excluding "well-known exposure routes" for this chemical and failing to provide an "overall assessment of risks." Contrary to SACC's explicit advice, EPA's draft risk evaluation excludes all human exposures from environmental releases of NMP, resulting in the absence of any consideration of environmental pathways that contribute to overall human exposure and risk. EPA	As described in Section 1.4.2, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA believes that coordinated action on exposure pathways and risks addressed by other EPA-administered statutes and regulatory programs is consistent with statutory text and legislative history, particularly as they pertain to TSCA's function as a "gap-filling" statute, and also

	excluded all risks that the general population faces from exposures due to releases of NMP to land, air, and water, based on the assumption that other statutes adequately address these exposures. No analyses or data have been presented, however, to show that other statutes are protective of the general population. For example, NMP is not currently regulated under the SDWA. It is also not listed as a HAP under the CAA. That means that there is no federal limit for NMP level in drinking water and that it is subject to only limited CAA regulations, which (unlike TSCA) do not encompass all known sources of the chemical and do not require the elimination of unreasonable risk. • This unlawful interpretation of TSCA has twice been rejected by the SACC and overlooks the widespread presence of NMP in environmental media to which millions of people are exposed. The exclusion of known exposure pathways violates both the intent and letter of TSCA. EPA is required to evaluate all such risks under TSCA, regardless of whether other statutes regulate them. In a recent decision on EPA's TSCA risk evaluation rule, the Ninth Circuit Court of Appeals ruled that EPA is unambiguously not granted the discretion "to exclude conditions of use, or their associated exposures and risks, from TSCA risk evaluations." If any of NMP's conditions of use results in air emissions or releases to water, these exposures are an essential part of the risk evaluation and must be considered by EPA, regardless of whether or not they might be addressed under other laws. • The releases and exposures that EPA is ignoring are far from trivial. EPA data on releases of NMP to air, water, and land for years 2015-2017 in the draft risk evaluation (p. 30) show that >9,500,000 lbs/year are released into	furthers EPA aims to efficiently use Agency resources, avoid duplicating efforts taken pursuant to other Agency programs, and meet the statutory deadline for completing risk evaluations. EPA has therefore tailored the scope of the risk evaluation for NMP using authorities in TSCA Sections 6(b) and 9(b)(1). EPA did not include exposures via the drinking water pathway or disposal to underground injection, RCRA Subtitle C hazardous waste landfills, or RCRA Subtitle D municipal solid waste (MSW) landfills in this risk evaluation, as these exposure pathways fall under the jurisdiction of other EPA-administered statutes and associated regulatory programs. The recent Ninth Circuit Court of Appeals decision in Safer Chemicals, Healthy Families v. EPA, 943 F.3d 397 (9th Cir. 2019) was limited to review of EPA rulemaking, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act*, 82 FR 33726 (July 20, 2017), commonly referred to as the TSCA Risk Evaluation Rule. As such, the Ninth Circuit decision did not opine on EPA's statutory authority under TSCA, as discussed above, to exclude conditions of use, or associated exposures and risks in TSCA risk evaluations. As described in Section 4.6.2.3 of the risk evaluation, EPA evaluated potential exposures and risks to the general population through ambient water, land-applied biosolids, and ambient air during problem formulation. Based on environmental fate properties of NMP and first-tier screening level analyses, EPA did not identify risk to the general population from these pathways. Specifically, EPA did not identify risks from human exposures that may result from contact with or ingestion of surface water, land releases of

	the environment. EPA's approach effectively reduces this quantity to zero. Excluding releases to air is also contrary to the EPA Problem Formulation, which said "[i]nhalation is expected to be a relevant route of exposure for the general population due to the propensity for NMP air releases from ongoing commercial and industrial activities." The most recent round of reporting for the TRI showed total NMP air emissions from 280 facilities of 1,532,507 million pounds in 2017 (an underestimate of total releases because emissions from small commercial operators below the TRI reporting thresholds are not captured). • EPA's exclusion of environmental releases that may be subject to other laws ignores the comprehensive multi-media scope of TSCA as framed by Congress. Residents of areas with a concentration of manufacturing and use facilities may also work at these facilities and be exposed to NMP both on the job and during non-work activities. Consumers who use NMP-based products may also be exposed to NMP air emissions, particularly if they live near emitting facilities, and may also be exposed to NMP through drinking water or proximity to waste sites. Similarly, workers exposed to NMP at their places of employment may also inhale NMP from ambient air or have dermal contact with NMP-containing products used in their homes, adding to their overall exposure. Determination of overall risk requires assessing exposure by all of these pathways in combination.	NMP (including those that may result from land-application of biosolids), or inhalation of outdoor air containing NMP released from industrial and commercial facilities. As the commenter notes, on p.36-37 of the problem formulation, EPA identified oral, dermal and inhalation exposures relevant to general population exposures. Based on subsequent screening level analysis in the problem formulation, EPA concluded (p47-48) that exposures through air, surface water, sediment, and land-applied biosolids do not require further analysis in the risk evaluation because exposure through these pathways is unlikely to present a risk concern. The final risk evaluation includes an updated screening level analysis of risks to the general population for incidental ingestion or dermal contact with NMP in surface water. EPA found no unreasonable risks to the general population from NMP under the conditions of use within the scope of the risk evaluation. EPA considered the reasonably available information and used the best available science to determine whether to consider aggregate or sentinel exposures for a particular chemical. EPA concluded that there is insufficient information about likely co-exposures to support analysis of aggregate exposure across multiple conditions of use. In Section 4.5 of the risk evaluation, EPA acknowledges that the decision not to aggregate risk across conditions of use could result in an underestimate of risk.
Consumer exposures		
SACC	**SACC COMMENTS:**	EPA appreciates the SACC's comments. Descriptions and justification on the consumer conditions of use can be found

	• The origin of the various consumer conditions of use is insufficiently justified in the draft risk evaluation and would benefit from further explanatory text. • Recommendation: Expand the justifications for each consumer condition of use, citing primary sources whenever possible, and conducting a sensitivity analysis on exposure factors.	in the documents preceding this risk evaluation, including the Scope of the Risk Evaluation for NMP and the NMP Problem Formulation. In the NMP Problem formulation EPA explained consumer conditions of use were identified through "extensive research and outreach, including review of published literature and online databases, SDSs, company websites and various databases. EPA met with environmental groups, chemical users, states, industry groups, companies and other stakeholders to identify consumer COUs."
SACC	**SACC COMMENTS:** • Consumer conditions of use in the draft risk evaluation assume limited frequency of use and a distinction between near-field (zone 1) and far-field (zone 2) exposures. Some activities, such as simultaneous hobby/craft work and childcare might lead to "child bystander" inhalation exposure to zone 1 air. Some small residences might also feature rapid mixing of air among rooms. The Committee was particularly concerned about households in which hobby/craft work is routine (*e.g.,* internet sellers deriving a significant portion of their income from "hobby/craft" activities). In such households, evaluation of chronic as well as acute exposures might be appropriate. • Recommendation: Treat enterprises co-located with residences as a distinct consumer condition of use and consider chronic exposures in that case.	EPA did not identify reasonably available information on chronic exposures to NMP that may occur in the home. EPA, however, did consider high-intensity users which would be consumers that use craft products in a greater amount for a longer duration. EPA also considered potential acute exposures to both adult and child bystanders resulting from acute exposures. This analysis of risks to bystanders is summarized in tables 4-49 and 4-50 in the risk evaluation.
51, 55	**PUBLIC COMMENTS:** • The draft risk evaluation only addresses developmental (fetal mortality) risks to consumers, ignoring potential effects on fertility on the grounds that "consumer exposure is not chronic in nature" (p. 160). The rationale for this approach is EPA's assumption that consumer exposure is limited to "a single use event which may	As stated above, EPA did not identify reasonably available information indicating chronic consumer exposures to NMP. EPA used product-specific data and consumer survey data to characterize the consumer activity patterns and use and exposure scenarios. The consumer survey data provides statistical range of data on the use of certain categories of products, including paint removers, adhesives, stains and

	occur over a 24-hour period" and that a "consumer uses a single product or product type" (p. 159). These assumptions, which EPA acknowledges may underestimate NMP exposures, disregard use scenarios for consumer products that could result in repeated NMP exposure over time. The draft risk evaluation identifies 12 separate categories of NMP-containing consumer products, representing 52 discrete products. (p. 140). Some of these products (adhesives, adhesive removers, paint removers, paints, , sealants, stains, and varnishes) would be expected to be used regularly by hobbyists, artists who work at home, or home renovators. Others (engine cleaners and degreasers and auto interior cleaners) would likely be used frequently by consumers who maintain and repair their own or friends' vehicles. Given the many different household functions performed by NMP-containing products, it is likely that many consumers use multiple products either simultaneously, resulting in greater acute exposures than addressed by EPA, or over time, resulting in chronic exposures that put them at risk of reproductive harm.	varnishes, degreasers and paints as outlined in the risk evaluation. EPA selected not only median but also high-end input parameters in order to develop a high-intensity use scenario to capture the exposures to those consumers who would use the products in greater quantities and for a longer duration such as arts and crafts hobbyists, do-it-yourself home renovators, or consumer auto repair hobbyists.
SACC	**SACC COMMENTS:** • The draft risk evaluation assumes that consumer products are less concentrated than industrial formulations. However, at least one Committee member objected, noting that consumers can acquire industrial formulations in many cases.	EPA identified consumer product concentrations based on information on SDSs for products available to consumers whether or not those products were formulated for consumers. For example, if a product was labeled 'for commercial use only' but could be purchased in a retail store or online retail platforms, it was included as a consumer product. However, some industrial formulations are not available through means normally available to consumers and can only be purchased through direct wholesale distributors. These formulations tend to be more concentrated than those sold in the retail space. For industrial products that are sold in retail space accessible to typical consumers, product labeling

		may be geared to the industrial or commercial use. Therefore, it is not always apparent the product would also meet the needs of the consumer and may decrease the likelihood of a consumer purchase.
SACC	**SACC COMMENTS:** • The current NMP risk evaluation may overestimate the number of minutes that children engage in mouthing behavior. EPA is referred specifically to Table 1 in Babich et al. (2004), which summarizes prior reports and regulatory defaults.	Table 1 of Babich et al., (2004) lists mouthing time/duration (in minutes per day) estimates from a variety of sources for PVC based teethers and toys. Since NMP data was found in children's blankets, EPA used the Consumer Exposure Model (CEM) exposure scenario for textile articles that are mouthed by children for mouthing durations cited in CPSC. These mouthing durations are within the ranges cited in Babich et al. (2004).
SACC	**SACC COMMENTS:** • Recommendation: Cite primary, rather than secondary, data sources whenever possible, and reference the work by Akesson and Jönsson (2000), Anundi et.al (1993), and Beaulieu and Schmerber (1991); they are not listed in the references section although exposure levels used in the evaluation seem to derive from these sources.	Where possible, EPA has revised the final risk evaluation to cite primary sources rather than secondary sources. For example, four primary sources cited in a secondary source have been added to Table 2-31 and to the text below this table for Paint and Coating Removers. Regarding the three specific sources suggested in this comment, the first source listed, Akesson and Jönsson (2000), is a primary source that is not reasonably available to EPA and is therefore cited in Table 2-31 and in the associated footnote. The second source listed, Anundi et.al (1993), was reviewed but not used for graffiti remover data. Instead, a robust data set in Anundi et al. (2000) was used for graffiti removers because the single, short-term data point in Anundi et.al (1993) was older and fell into the range of the newer data. The third source listed, Beaulieu and Schmerber (1991), contained data for the microelectronics industry are over 30 years old and were not used due to availability of a robust and more relevant recent data set less than 10 years old.
51, 55	**PUBLIC COMMENTS:** • EPA's Problem Formulation for NMP cites evidence from two Canadian studies that use of NMP-containing	The risk evaluation accounts for consumer exposure to NMP through air. EPA used the Consumer Exposure Model to estimate air concentrations associated with each consumer

	products in homes and buildings results in elevated levels of NMP in indoor air (p. 33). Although the Problem Formulation commits (p. 58) to further "[e]valuate the indoor exposure pathways based on available data," the draft risk evaluation itself makes no mention of NMP levels in indoor air. Elevated NMP concentrations in indoor air would represent another contributor to chronic consumer exposure, adding to direct dermal and inhalation exposure from product use.	exposure scenario. Those concentrations were then used as inputs in the PBPK model used to predict total internal exposures (blood concentrations). Exposures predicted for bystanders of consumer users are based on air concentrations alone since no dermal contact is anticipated. EPA did cite NMP air concentration monitoring data after paint removal use (NIOSH, 1993), compared that to modeled NMP air concentration and found the two were relatively similar and not a risk to non-users.
33, 57	**PUBLIC COMMENTS:** • Many exposure assumptions overestimate actual exposures. • To ensure that the range of expected exposures to NMP by consumers is accurately characterized, EPA should account for the most likely exposure scenarios, which involve product use in outdoor and/or garage settings (ABT, 1992). • For the small, unventilated room scenarios, two additional options should be included to account for higher air change rates associated with "Window Open" and "Exhaust Fan On." • For consumer and worker exposure scenarios that are inconsistent with product labeling instructions, these should be presented separately as "Product Misuse Scenarios" so that risk management options for these scenarios can be addressed independently from "Product Use Scenarios."	EPA modeled medium-intensity use of each of the consumer product scenarios to provide information for most prevalent exposures. Table 2-78 in the risk evaluation lists the various locations where the consumer product was modeled to be used. For example, EPA modeled a deck adhesive product to be used outdoors, though adhesives could be used anywhere inside a home as well and modeled engine degreasing use in the garage. EPA is also concerned about high-intensity consumer use as they represent a fraction of the population that would be more highly exposed, such as do-it-yourself paint removal or engine repair where longer duration of use and a greater amount of the product are anticipated. Given that there are plenty of reasons for a consumer not to open windows (cold or very hot weather) or use an exhaust fan (not available in most rooms other than bathrooms), EPA chose not to include these scenarios in the current risk evaluation. For consumer exposure, there were no "product misuse scenarios" considered.
33, 57	**PUBLIC COMMENTS:**	EPA conducted quality control of all Consumer Exposure Model inputs and outputs.

	• EPA should conduct a strong quality assurance/quality control check to ensure that any errors on Csat and other parameters are corrected and implemented appropriately in the Consumer Exposure Model (CEM).	
33, 57	**PUBLIC COMMENTS:** • The saturation of air with NMP is dependent upon humidity, and Csat is negatively correlated with humidity. A relative humidity of 50% would correspond to a Csat value of approximately 525 mg/m^3, which is considerably lower than the value assumed by EPA. • The distribution of relative humidity in indoor air in the United States (*e.g.*, low, average, and high humidity values of ~15%, ~50%, and ~85%) should be characterized based on recent surveys (*e.g.*, USHUD, 2010) and incorporated into the risk assessment to characterize a distribution of Csat values based on the relationships described (*e.g.*, 1,030, 525, and 132 mg/m^3) for indoor air modeling. • Separate assumptions for relative humidity should be made for the use of aqueous vs. non-aqueous NMP products separately, to avoid an unrealistic assumption of low humidity following application of aqueous NMP products. • EPA's assessment does not consider condensation and aerosol droplet formation for concentrations of NMP vapor exceeding 470 mg/m^3 (or 116 ppm). • In EPA's 2015 assessment, a Csat value of 640 mg/m^3 was considered, but this value is not considered in the current risk evaluation; no explanation is provided.	Since publication of the 2015 Paint Remover Risk Assessment, EPA changed the NMP vapor pressure from 0.190 to 0.345 mm Hg which has affected the Csat value. The estimated Csat calculated from CEM is now 1.84E+3 mg/m^3, using a vapor pressure of 0.345 mm Hg. In this instance, the high intensity use Engine Degreaser scenario would not meet Csat. EPA varied the three most sensitive variables used in the Consumer Exposure Model to predict consumer exposures: weight fraction, mass of product and duration of product use. From these exposure model results, EPA presents in the risk evaluation, the medium-intensity and high-intensity use scenarios. The high-intensity use scenario captures the highest duration of use, highest mass and highest average weight fraction and represents an upper end of the expected consumer exposures to NMP even with other variables such as humidity constant. For EPA's NMP consumer exposure estimates, the PBPK model was used to estimate total blood concentration from dermal contact, vapor-through-skin, and inhalation of NMP during product use. EPA modeled exposure to NMP during consumer product use (with limited duration for most products) and then inhalation exposures within the rest of the house for 24 hours. EPA anticipates that if there is already significant dermal contact with the liquid, the amount of aerosol would likely only add a small increment of exposure.

57	**PUBLIC COMMENTS:** • EPA should carefully review the inconsistency of the values from the exposure models used for CEMs versus those used for worker exposures [Chemical Screening Tool for Exposures and Environmental Releases (ChemSTEER)] as there seem to be fundamental differences in the underlying assumptions.	EPA uses different models for different exposure scenarios. The assumptions for ChemSTEER are specific to occupational scenarios, whereas CEM is for consumer exposure scenarios. For example, for consumer exposure, there is no assumption of glove use, there are specific parameters associated with indoor homes such as air exchange rate, activity patterns (time spent using the consumer product as well as time inside the house and outside of the house) that are inherently different from occupational scenarios. For this risk evaluation, the only parameter values in common for both consumer and occupational scenarios are adult body weights and hand surface areas, and these values are consistent.
57, 33	**PUBLIC COMMENTS:** • The relative magnitude of the air concentrations modeled for consumer exposures (*e.g.,* peak concentrations up to 1,300 mg/m^3; 24-hour TWA up to 103 mg/m^3) compared to worker exposures (*e.g.,* 8-hour TWA up to 64 mg/m^3) is counterintuitive. • EPA should identify differences in key assumptions and where possible, consider that the application of the more reasonable predictions of the ChemSTEER model be adopted for consumer scenarios that are comparatively similar.	There are assumptions in consumer exposure scenarios that are inherently different from those of occupational scenarios. For example, there may be occupational scenarios that include industrial-sized facilities with ventilation, which is not an assumption in consumer scenarios. Thus, given the specific consumer product, it's duration of use and room of use, it is reasonable to have a higher air concentration than that found in an occupational setting. EPA uses different models for different exposure scenarios. The assumptions for ChemSTEER are specific to occupational scenarios, whereas CEM is for consumer exposure scenarios. For example, for consumer exposure, there are specific parameters associated with indoor homes such as air exchange rate, activity patterns (time spent using the consumer product as well as time inside the house and outside of the house) that are inherently different from occupational scenarios. For this risk evaluation, the only parameter values in common for both consumer and

		occupational scenarios are adult body weights and hand surface areas, and these values are consistent.
PPE		
SACC	**SACC COMMENTS:** • Recommendation: EPA should use the authority provided under the new TSCA rules to obtain better information whenever data in the open literature are found to be sparse (*e.g.*, worker and ONU practices and exposures from manufacturers and processors, empirical data to support the specific condition of use modeling results and increase support for occupational exposure estimates, consumer exposure data, data on NMP content in consumer products, etc.). • Recommendation: Contact the State of California Air Resources Board for their data on NMP content in consumer products. • It was noted that the State of California has established a PEL for NMP, so some data should be available there. • The literature underpinning the American Conference of Governmental Industrial Hygienists Biological Exposure Indices for NMP should also be examined to see if any useful data exist there. • One Committee member suggested that exposure to skin beyond hands was likely for many occupational conditions of use and that some useful data with respect to skin exposure might be gleaned from studies sponsored by the Agricultural Handlers Exposure Task Force.	EPA obtained and considered reasonably available information, defined as "information that EPA possesses, or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines . . . for completing such evaluation." Given the timeframe for conducting risk evaluations on the first 10 chemicals, use of TSCA data gathering authorities has been limited in scope. In general, EPA intends to utilize TSCA data gathering authorities more routinely for the next 20 risk evaluations. EPA reviewed the California Air Resources Board (CARB) and CalOSHA websites for additional NMP occupational air monitoring data and did not find relevant data. EPA reviewed the *n*-Methyl-2-Pyrrolidone: BEI(R) 8th Edition Documentation published by the American Conference of Governmental Industrial Hygienists and found no new data. This documentation did refer to data in one field study, Anundi et al, 2000, which is cited in the risk evaluation and its data used. EPA reviewed the Agricultural Handlers Exposure Task Force website for data related to NMP and did not find any relevant data. The information from this source includes a database of doses, provided in mg or ug of exposure per pound of pesticide applied. The information also includes PPE assumptions and frequency of application. The source does not provide PBPK inputs needed for NMP assessment, such as air concentrations, exposure duration, or surface area exposed.
51, 34, 49, 61	**PUBLIC COMMENTS:** • EPA lacks sufficient exposure/monitoring data to support proposed findings of no unreasonable risk. EPA's	EPA obtained and considered reasonably available information, defined as "information that EPA possesses, or can reasonably obtain and synthesize for use in risk

	evaluation of workplace risks from NMP exposure is flawed because it relies on limited worker exposure data. EPA has substantial authority under TSCA sections 4, 8, and 11 to require the submission of existing exposure information, as well as additional monitoring or testing to fill data gaps. Thus far, however, EPA has not exercised that authority for any of its risk evaluations. It has also failed to ask employers to share the workplace monitoring data that they are required to preserve under OSHA regulations, or asked OSHA and other state and federal agencies to provide access to the extensive exposure information in their direct possession. In finalizing the NMP risk evaluation, EPA should make every effort to obtain additional workplace monitoring data from OSHA, state agencies, and industry.	evaluations, considering the deadlines . . . for completing such evaluation." EPA selected the first 10 chemicals for risk evaluation based in part on its assessment that these chemicals could be assessed without the need for regulatory information collection or development. Given the timeframe for conducting risk evaluations on the first 10 chemicals, use of TSCA data gathering authorities has been limited in scope. In general, EPA intends to utilize TSCA data gathering authorities more routinely for the next 20 risk evaluations. In the 2017 Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act (82 FR 33726, July 20, 2017), EPA committed to, by codifying, interagency collaboration to give the public confidence that EPA will work with other agencies to gain appropriate information on chemical substances. This is an ongoing deliberative process and EPA is not obligated to provide descriptions of pre-decisional and deliberative discussions or consultations with other federal agencies. In the interest of continuing to have open and candid discussions with our interagency partners, EPA is not intending to include the content of those discussions in the risk evaluation. For the NMP risk evaluation, EPA reviewed and integrated NMP monitoring data from the OSHA Chemical Exposure Health Data (CEHD) database (OSHA, 2017), specifically for the following OESs: Other electronics (capacitor, resistor, coil, transformer, and other inductor) manufacturing (Section 2.4.1.2.9), printing (Section 2.4.1.2.11), and spray/ wipe cleaning (Section 2.4.1.2.16). Additionally, EPA requested NMP monitoring data from OSHA and did not receive any additional data to supplement the CEHD data. EPA also requested and received NMP monitoring data from the DoD, specifically for paint removal and spray application of paint containing NMP. EPA did not integrate these data

		into the assessment due to lack of metadata resulting in a confidence rating below other monitoring data used in the assessment. These data are included and discussed in Appendix A of the Supplemental File on Occupational Exposure Assessment.
53	**PUBLIC COMMENTS:** • EPA should gather additional data or provide further explanation related to identified issues in the final risk evaluation, particularly related to air concentrations and exposure times during formulation of products with NMP, application, and use of relevant products for both consumers and workers and laboratory use.	EPA reviewed additional sources recommended by the SACC and public comments. For occupational exposures, EPA has added and integrated the relevant information into the assessment. This occupational exposure data and information includes air concentration data and durations of tasks and shifts for formulation, printing, electronics manufacturing and cleaning. EPA also reviewed data for consumer products and made adjustments to the final risk evaluation. For example, EPA reviewed paint remover formulations and revised the high-intensity use scenario to include paint removers with 60% NMP, instead of 50% NMP.
SACC	**SACC COMMENTS:** • Discuss the efforts made (if any) to obtain sample-relevant data when not reported (generally designated as unknown in tables) by the sources of the data.	EPA may seek critical sample-relevant metadata on a case-by-case basis if its provision would significantly impact the occupational exposure assessment. For NMP, EPA was not aware of data in need of additional sample-relevant metadata where its provision would significantly impact the occupational exposure assessment.
SACC	**SACC COMMENTS:** • One Committee member found the description of the actual amount of data available for specific occupational exposure scenarios inadequate. Estimates of central and high-level exposures based on just two samples are highly uncertain, even if the analytical quality of the data is high. • The draft risk evaluation does not describe a systematic and robust protocol for determining when the available measurements are sufficient to derive estimates of exposure for an occupational exposure standard with	Table 4-47 provides a summary of actual amounts of air monitoring data and of model estimates for each OES. Table 4-48 provides a summary of dermal parameter data and assumptions for each OES. For occupational exposure estimation, EPA uses data sets of most sizes due to the prevalence of data scarcity. EPA uses modeled estimates according to the data integration strategy described in Appendix C of the Supplemental File on Occupational Exposure Assessment. This appendix indicates that EPA uses data with the highest quality ratings and may

	reasonable reliability. Clarify how EPA decides when there is enough good quality data to derive a sufficiently reliable estimate of exposures for specific scenarios. The risk evaluation should discuss why and where very few data were used instead of modeling estimates. • Procedures used in estimating air concentrations when data are very sparse should be clarified and standardized. • Recommendation: Describe the protocol used for dealing with parameter estimation when few actual exposure measurement data points are available and describe the protocol for deciding to use modeled values rather than available measurements.	supplement the highest quality data with data of lower quality when warranted. This appendix also discusses the factors, including dealing with few measurements or samples or using modeled values or assumptions, for assigning confidence ratings for PBPK input parameter sets.
Clarification/rationale/justification needed		
SACC	**SACC COMMENTS:** • Clarity on how central and upper exposure tendencies were derived is needed. The risk evaluation needs to be more explicit about uncertainties in these estimates since the risk evaluation assumes that workers and ONUs have similar central tendency inhalation exposures.	In Section 2.4.1.1, EPA explained for occupational exposures how EPA selected grouped sets of individual input parameter values intended to represent central tendency and high-end occupational exposure scenarios. EPA clarified in all OES subsections of 2.4.1.2 that EPA assigns the same confidence level for PBPK inputs for both workers and ONUs because lower surface areas for liquid contact for ONUs have higher certainty but air concentrations experienced by ONUs have lower certainty. These factors offset one another in determining ONU confidence level using worker confidence level as a starting point. In Section 2.4.1.4, EPA is explicit in the discussions of uncertainties of individual parameters. Also, EPA modeled exposures for workers and ONUs using both central tendency and high-end air concentrations.
SACC	**SACC COMMENTS:** • Material sourced from the paint strippers work plan document should have been sourced from original literature for the sake of clarity.	EPA added the citations to the original reference sources from the paint strippers work plan document in Section 2.4.1.2.8 and in the Supplemental File on Occupational Exposure Assessment.

SACC	**SACC COMMENTS:** • Provide the rationale for assigning medium reliability for exposure estimates assuming PPE use when the Agency acknowledges that information on glove use is lacking.	In Chapter 2 and in the Supplemental File on Occupational Exposure Assessment, EPA has removed assignments/ assumptions of specific glove PFs to apply to each OES. Table 2-77 has been updated to include worker exposures for all glove PFs for all OESs. EPA clarified the uncertainties of PF values in the overall confidence rating discussion at the end of each OES subsection in Section 2.4.1.2. Additionally, EPA added Appendix C of the Supplemental File on Occupational Exposure Assessment, which describes how various factors including the glove PFs impact the confidence of the PBPK inputs.
SACC	**SACC COMMENTS:** • Provide clarification on how specific scenarios were mapped to subcategories and categories of use across multiple industries (NMP risk evaluation, Sections 1.4.1 and 2.4).	In Section 2.4, EPA clarified how the conditions of use listed in Table 1-6 were crosswalked to the occupational and consumer exposure scenarios assessed in this report provided in Table 2 2: EPA crosswalked/mapped the exposure scenarios to conditions of use using professional judgment based on reasonably available data and information.
Consumer confidence ratings		
SACC	**SACC COMMENTS:** • Some committee members questioned why all consumer scenarios have the same level of overall confidence. The extent to which this single input is driving the level of confidence was questioned and it was suggested that some type of sensitivity analysis might better quantify confidence.	As described in Section 2.4.2.6, there is an absence of direct measurement and monitoring of consumer exposures to NMP. Exposure estimates for consumers are therefore all based on modeling approaches that rely on similar sets assumptions with similar sources of uncertainty. This results in similar levels of overall confidence across all consumer exposure scenarios.
Occupational confidence ratings		
SACC	**SACC COMMENTS:** • Recommendation: Tabulate specific condition of use factors influencing confidence levels in a manner analogous to tables of input parameters (NMP risk evaluation, Table 2-66) and exposure results (NMP risk evaluation, Table 2-67), in order to increase transparency.	EPA clarified in the introductory paragraphs of Section 2.4.1.2 that key strengths and limitations of each PBPK input parameter set are listed and used to determine qualitative overall confidence ratings, and these lists and ratings are provided at the end of each OES subsection as well as clarifying that the occupational exposure data integration strategy and factors impacting the overall confidence ratings

		are available in Appendix C of the Supplemental Information on Occupational Exposure Assessment. EPA added explanations of the factors impacting qualitative confidence ratings and their directional influence in this appendix. EPA does not have a feasible design for such a tabular summary of factors and directional influence for each OES, which would essentially duplicate the paragraphs at the end of each OES subsection in 2.4.1.2.
Uncertainty assessment		
SACC	**SACC COMMENTS:** • Some Committee members expressed dissatisfaction with the qualitative treatment of uncertainty in the draft risk evaluation, preferring a more formal probabilistic approach. • Recommendation: Perform more extensive uncertainty assessment, including clearly discussing the uncertainties related to the assumptions used in the draft risk evaluation. These uncertainties should be discussed in context of choice of the MOE.	EPA considers the uncertainties associated with each condition of use, and how the uncertainties may result in a risk estimate that overestimates or underestimates the risk. Based on such analysis in part, EPA determines whether or not the identified risks are unreasonable. To the extent possible, EPA has characterized uncertainties related to exposure, hazard, and risk. EPA lacks reasonably available information to quantify all sources of uncertainty. Sources of uncertainty that can be quantified are described quantitatively, but those for which information is lacking are described qualitatively. EPA has inserted additional discussion of the sources of uncertainty related to PBPK modeling of exposure estimates in Section 4.3. Regarding occupational inputs to PBPK exposure modeling, EPA has fully explained uncertainties in Section 2.4.1.4. While most uncertainties in occupational inputs can't be quantified, this section does address directional impacts of uncertainties to the extent feasible. EPA also varied occupational inputs to the extent feasible. EPA added a new qualitative sensitivity discussion on modeling to Appendix B of the Supplemental Information on Occupational Exposure Assessment. Benchmark MOEs are selected based on the total uncertainty factors associated with the hazard POD and they do not

		account for uncertainty around potential human exposure estimates. Uncertainty and variability related to human exposure are captured in the various assumptions used to derive exposure estimates.

5. Human Health Effects

Human Health Effects		
Charge Question 4.1: Please comment on the reasonableness of the evaluation of human health hazards. Are there any additional NMP specific data and/or other information that should be considered? **Charge Question 4.2:** Please comment on the conclusions presented regarding the genotoxic and carcinogenic potential of NMP. **Charge Question 4.3:** Please comment on the validity of endpoints selected as the basis for PODs and their relevance to the evaluation of human health risks across lifestages. **Charge Question 4.4:** Please comment on the strength of evidence for, and general applicability of fetal mortality (resorptions) for evaluating the human health risks associated with acute exposure to NMP. **Charge Question 4.5:** Please comment on the strength of evidence for, and the general applicability of decreased fetal/pup body weight or decreased fertility for evaluating the human health risks associated with chronic exposure to NMP. **Charge Question 4.6:** Please comment on whether the document adequately identified uncertainties, assumptions, and data gaps associated with the selected PODs and whether the analysis addressed them sufficiently.		
#	**Summary of Comments for Specific Issues Related to Charge Question 4**	**EPA Response**
Hazard identification - Additional information to include or exclude		
SACC	**SACC COMMENTS:** • Recommendation: Include more detailed summaries and describe the context of all studies that were only briefly summarized in the risk assessment studies referenced in the current NMP risk evaluation. • Recommendation: Clearly state how summaries of studies where full text is unavailable are being used in health hazard identification and risk characterization. • The draft risk evaluation cites past draft risk assessments of NMP performed by EPA (2015) and the Organisation for Economic Cooperation and Development (OECD, 2007). Some of these previous documents contained summaries of studies to which the Committee did not have full access to. Several Committee members concluded that these data should not be considered (*e.g.*,	The studies that are the basis for quantitative analysis in hazard characterization are available to EPA and the public. Other studies were not fully available to EPA. EPA acknowledged results presented in summaries of these studies, but did not rely on results summarized by secondary sources for dose-response information. Where possible, EPA has revised the final risk evaluation to cite primary sources rather than secondary sources and to be more transparent about which studies are available to EPA and have gone through data quality review. For example, in the genotoxicity section EPA has inserted data quality ratings for studies that were available to EPA. While EPA acknowledges and has reviewed summaries of additional studies, conclusions on genotoxicity are based on information in the studies that were fully available to EPA.

	be given 0 weight in the weight of evidence [WOE]), since the ability to peer review the risk evaluation requires independent analysis of all underlying data, and that is not possible with data from summary-only sources. • Genotoxicity and cancer studies were available only as summaries for review. The committee was unable to validate the interpretation of cancer data provided in Table 3-6 because the data were not provided or available in supplemental files	The cancer studies summarized in Table 3-6 (Malley et al., 2001; Lee et al., 1987) were available to EPA as unpublished study reports but results of these studies are also available to EPA and the public as peer-reviewed papers published in scientific journals. Footnotes to the table cite the unpublished studies that correspond to these published studies.
SACC	**SACC COMMENTS:** • Recommendation: Consider using information not otherwise useful for POD derivation for qualitative supporting evidence in the evidence integration phase of the risk evaluation.	EPA includes several studies in the evidence integration portion of the assessment that provide qualitative evidence even though they are not able to inform dose-response analysis. These include studies that report developmental neurotoxicity and developmental toxicity but only evaluate effects of single high doses (Hass et al., 1995; Hass et al., 1994), the case report of acute maternal effects and pregnancy loss at 31 weeks following an accidental occupational exposure to NMP (Solomon et al., 1996), and a study with rat whole embryo cultures that provides additional evidence of embryotoxicity (Flick et al., 2009). While these studies do not provide quantitative information sufficient to support derivation of a POD, they are discussed in Section 3.2.4 (Weight of Scientific Evidence) of the risk evaluation and contribute to the overall weight of the scientific evidence.
SACC	**SACC COMMENTS:** • Recommendation: Include human data from the worker studies, including Haufroid (2014). • With respect to adult neurotoxicity, it is important to include the results from the Haufroid (2014) worker study that identifies neurotoxicity as an impacted health endpoint.	In response to this comment, EPA reconsidered human evidence from the Haufroid et al. (2014) paper as well as the Nishimura (2009) study, both of which were evaluated using EPAs systematic review data quality criteria. The Haufroid 2014 study was primarily focused on evaluating the efficacy of biomarkers of exposure to NMP. Evaluation of neurotoxicity in this study was limited to self-reported

		symptoms in response to a survey. In addition, the sample size for currently exposed individuals was very small (n=8) while other study participants (n=22) were recalling past exposures and symptoms. The study did not find any association between NMP exposure and any of the health effects evaluated, including neurotoxicity. As stated by the authors, "the number of symptomatic (work-related or not) cases was mostly low (below 10 or even 5 in each cell) making interpretation quite difficult and consideration of possible confounders impossible." The Nishimura (2009) study also has a limited sample size (n=14 exposed workers). It included some clinical neurobehavioral endpoints in addition to survey responses. The study found no significant association between occupational exposure and any of the clinical endpoints. The mean score on the self-rated depression scale was significantly lower in exposed workers relative to controls, but the study reports that NMP exposure did not contribute to SDS in multiple regression analysis. Overall, EPA concluded that the human health hazard information provided by these small occupational studies is limited and difficult to interpret. In response to this comment, EPA inserted a brief reference to these studies in the hazard identification portion of the risk evaluation: "Two cross-sectional occupational epidemiology studies report no significant association between NMP exposure and neurobehavioral endpoints, but very small sample sizes and limitations in study design (including reliance on self-reported effects for many endpoints) make it difficult to interpret these results (Haufroid et al., 2014; Nishimura et al., 2009)."

Hazard identification - Irritation and sensitization		
SACC, 32	**SACC COMMENTS:** • Recommendation: Provide better characterization of dermal exposure studies and reevaluate if available data are sufficient to determine if NMP is an irritant or sensitizer. • Recommendation: Identify the inefficient assessment of NMP-induced irritation/sensitization in the available literature as a data gap. • The Committee indicated concern with the inaccurate categorization of study results to "Irritation and Sensitization" and "Immune Toxicity." These are terms which could be misleading, adding confusion to the risk evaluation. • Most studies employed oral or inhalation routes of exposure, but one of the major routes of exposure for humans is dermal. Therefore, the Evaluation should discuss whether absorption of NMP via oral, inhalation and dermal routes results in similar **PUBLIC COMMENTS:** • EPA should conduct a more thorough evaluation of the evidence, including consideration of data quality and human relevance, to better characterize potential irritant and sensory effects.	EPA has slightly modified the narrative around irritation to be more specific. The final risk evaluation makes clear that there is not enough data to determine whether NMP is an irritant or skin sensitizer, stating, "Limited data from secondary sources suggesting that NMP is not a sensitizer (RIVM, 2013; Lee et al., 1987) are insufficient to support conclusions on sensitization with a high degree of confidence." EPA identifies the limited data on sensitization as a source of uncertainty in Section 3.2.6. As described in Section 3.2.2 on toxicokinetics and Section 3.2.5.5 on derivation of internal doses, the available toxicokinetic studies demonstrate that NMP readily enters systemic circulation following inhalation, dermal and oral exposures. EPA assumed that once NMP enters systemic circulation, all routes of exposure result in similar distribution. The revised risk evaluation includes this additional description of evidence for distribution to tissues from systemic circulation: "In rats administered a single intravenous dose, NMP was distributed to all major organs with the highest concentrations detected in the liver and intestines (Wells and Digenis, 1988)." In the PBPK models EPA used to establish PODs and estimate human exposures, distribution of NMP to tissues is assumed to be flow-limited.
Hazard identification - Developmental neurotoxicity		
SACC, 38	**SACC COMMENTS:** • Recommendation: Integrate the Hass et al. (1994) study findings in the WOE discussion on developmental toxicity. **PUBLIC COMMENTS:**	The Hass et al., 1994 study is included in the WOE discussion on developmental toxicity and was considered in the dose-response portion of the risk evaluation (*e.g.,* see Table 3-8 and Figure 3-4). EPA has inserted a statement about the neurodevelopmental effects reported in Hass et al 1994 into the Weight of Evidence section for developmental toxicity: "Hass et al. (1994) also reported

	• EPA should regulate NMP as a developmental neurotoxic agent, with potential lasting adverse effects on neurological functioning.	neurodevelopmental effects following inhalation exposure during gestation. The effect was evaluated at a single dose and has not been evaluated in other studies, resulting in a lack of information about potential neurodevelopmental effects at lower exposure concentrations." As stated in the risk evaluation, "Effects on postnatal neurological behavior were reported following whole-body inhalation exposure to 151 ppm (612 mg/m^3) NMP during gestation (Hass et al., 1994). However, because behavioral effects were only evaluated at this single exposure level, no NOAEL has been identified for developmental neurotoxicity and dose-response for this endpoint cannot be characterized." In the absence of other data evaluating potential neurodevelopmental effects of lower levels of NMP, EPA is unable to further evaluate this endpoint or incorporate it into dose-response assessment, but it does contribute to the overall weight of the scientific evidence. EPA acknowledges the absence of other data on developmental neurotoxicity as a source of uncertainty in the risk evaluation.
Hazard identification - Scope and data gaps		
51, 34, 38	**PUBLIC COMMENTS:** • EPA should address all NMP-related health endpoints – neurotoxicity, liver and kidney effects, immunotoxicity, and developmental and reproductive harm – in its final risk evaluation or provide a detailed science-based justification for retaining its current narrow approach. • EPA is obligated under TSCA to obtain and assess the information necessary to determine whether health effects that are now poorly characterized present unreasonable risks of injury. The proper time to take these steps is before EPA initiates a risk evaluation.	EPA evaluated the reasonably available information from animal toxicology studies and narrowed the scope of its hazard identification based on the available evidence. While EPA summarized reasonably available evidence for other health endpoints, the systematic review process and weight of the scientific evidence discussion are focused around endpoints that have been identified previously as primary targets of NMP. While EPA agrees that there is limited information on some endpoints, EPA considers the database adequate for risk evaluation without the need to separately address immune effects on their own.
SACC, 51	**SACC COMMENTS:** • The Committee wondered if NMP is an immunotoxicant.	EPA evaluated the reasonably available information from animal toxicology studies. While EPA agrees that there is

	The Committee concluded that available data are unsuitable for determining dose-response for immunotoxicity because of use of outcomes that may or may not derive from an immune reaction cascade and study timeframes representing acute, not chronic, exposures. **PUBLIC COMMENTS:** • The insufficiency of immunotoxicity data should be considered a data gap for NMP. EPA should use its information gathering authorities to fill this data gap.	limited information on immunotoxicity, EPA considers the database adequate for risk evaluation without the need to separately address immune effects on their own. EPA identifies the limited data on immunotoxicity as a source of uncertainty in Section 3.2.6.
SACC	**SACC COMMENTS:** • Recognize and directly state that some endpoints such as cardiometabolic and endocrine are not able to be adequately assessed given the WOE.	EPA considers the database adequate for risk evaluation without the need to separately address cardiometabolic and endocrine effects on their own. EPA revised Section 3.2.6 and Section 4.3.5 on Human Health Hazard Assumptions and Uncertainties to specifically identify the limited data on sensitization, immunotoxicity, cardiometabolic effects, endocrine effects, and developmental neurotoxicity as sources of uncertainty that may result in an underestimate of risk.
Hazard Identification - Maternal toxicity		
SACC	**SACC COMMENTS:** • Recommendation: Evaluate maternal systemic toxicity as a separate and distinct endpoint from fetal toxicity. • Committee members felt that there was evidence supporting both maternal systemic toxicity as well as fetal toxicity in the studies provided, but that it is difficult to distinguish between developmental and maternal toxicity given the data presented.	An integrated assessment of developmental and maternal toxicity was conducted, in accordance with Agency policy (U.S. EPA, 1991). Since EPA and OECD guideline prenatal developmental and reproductive toxicology studies are designed to include doses that are maternally toxic, this is not an uncommon issue. For studies in which developmental outcomes are observed at doses that are not excessively toxic in the dam, current information is inadequate to assume that developmental effects are the result only of maternal toxicity. When the developmental LOAEL is the same for the adults and offspring, it might be because both the adult and developing organisms are sensitive at that dose level. Even if the effect in the developing organisms are secondary to

		maternal toxicity, the effects might be reversible in adults (*e.g.*, body weight deficits) yet permanent or of greater severity in the offspring (*e.g.*, death). Furthermore, no additional information, *e.g.*, as recommended in Beyer et al. (2011), was identified that would further elucidate the contribution of maternal toxicity to developmental outcomes for the available studies. Interestingly, the OECD had reviewed available developmental and reproductive toxicology studies for NMP in the course of implementation of the HPV Programme, noting that maternal toxicity had been observed at treatment levels that were maternally toxic. Notably, the OECD NMP report specifically concluded that "developmental effects are not considered secondary to maternal toxicity" (OECD, 2007).
SACC	**SACC COMMENTS:** • Recommendation: Include a discussion of the uncertainties and assumptions relating to differentiating maternal and fetal toxicity and with the choice of fetal mortality or resorption as the endpoint for acute exposure.	Section 4.3.5 includes a discussion of the uncertainties related to reported effects on maternal body weight in some of the developmental studies considered in hazard characterization.
54	**PUBLIC COMMENTS:** • Given that doses in the Saillenfait et al. (2002, 2003) studies resulting in statistically significant increases in fetal mortality were the same or higher than doses causing maternal toxicity, EPA should consider re-evaluating the fetal mortality POD. At the very least, EPA should provide additional discussion of this issue.	As described in Section 4.3.5, "The maternal effect reported in the Saillenfait (2003) inhalation study (transient decrease in body weight gain and food consumption) has been cited as a confounding factor by some study authors. EPA does not concur with this assertion, specifically as it relates to the observed decrease in maternal body weight gain on GD 6-21 (minus gravid uterine weight). Although a decrease in maternal body weight gain was observed, it is not statistically significant. Dams weighed roughly 235 g at GD 0, and whereas the controls gained approximately 32 grams, the high dose dams gained slightly less, roughly 26 grams. Given the lack of significant change in maternal body weight gain, it is

		unlikely that the observed decreases in fetal and pup body weights reflect a secondary effect of maternal toxicity. In other key and supporting studies, including an inhalation study (Solomon et al., 1995; E. I. Dupont De Nemours & Co, 1990), and an oral gavage study (Saillenfait et al., 2002), similar decreases in pup body weight were observed at similar exposure levels, in the absence of any effects on maternal body weight."
Hazard Identification - Carcinogenicity		
SACC, 48, 51, 34	**SACC COMMENTS:** • Recommendation: Although not considered a most sensitive health effect associated with NMP exposures, a WOE carcinogenesis summary should be added to the risk evaluation. • Recommendation: Recognize that there is evidence that NMP has mitogenic properties while acknowledging that there are not enough data to conclude whether NMP is a promotor. • The Committee was split on whether there are enough data to draw the conclusion that there is no carcinogenic potential from NMP exposures. Several Committee members noted that there is evidence of effects in the current data, including neoplasms at multiple stages and evidence of stimulatory proliferation, and others suggested that additional testing must be done in at least one other species besides the rat to be confident in making this determination. Some Committee members indicated that while these data are not strongly suggestive of carcinogenicity, they do have some positive findings that should not be disregarded and should be noted in the report. • Some data suggest that a dose-response may be nonlinear	In response to these comments, EPA has inserted a summary or conclusions in Section 3.2.3.2.2 and the following Weight of Evidence for Carcinogenesis summary to the evaluation (Section 3.2.4.2): "The reasonably available scientific information does not provide strong evidence for carcinogenicity. Inhalation exposure studies are more relevant to human exposure scenarios than oral exposure studies. The inhalation cancer bioassay (Lee et al., 1987) reported a significant increase in pituitary adenocarcinoma incidence in rats at the middle dose after 18 months of exposure, but no significant effect after 24 months of exposure and no effect at the highest dose. The lack of dose-response relationship makes it difficult to determine that effects are related to exposure and prevents quantitative dose-response analysis. In oral dietary studies (Malley et al., 2001), there was no significant association between NMP exposure and increased tumor incidence in rats. There was a small but significant increase in liver tumor incidence in male, but not female mice. While some evidence is suggestive of a potential cancer risk at maximally tolerated doses, the data are inconsistent and do not demonstrate a clear dose-response relationship. In addition, available in vivo and in vitro studies report no evidence of genotoxicity. The reasonably available data is insufficient to support a

	with a threshold (Nohmi, 2018). The potential for a non-monotonic dose response is not discussed in the risk evaluation. **PUBLIC COMMENTS:** • There is no apparent reason for disregarding the Malley et al. (2001) findings. This study should have been considered evidence supporting the determination that NMP poses a risk of cancer. Toxicological evidence of cancer should not be dismissed on the basis that it occurs only in the high dose group, unless it is accompanied by evidence of excessive toxicity. • The final NMP evaluation must fully address the evidence of NMP carcinogenicity and make a determination of unreasonable risk for this endpoint using a linear low-dose extrapolation unless it can provide convincing evidence of an MOA that is not relevant to humans (*i.e.*, peroxisome proliferation).	quantitative evaluation of cancer risks from NMP and EPA did not further evaluate cancer risks in the dose-response assessment or risk characterization."
POD derivation - Clarification of doses used		
SACC	**SACC COMMENTS:** • Recommendation: Clarify whether maternal or fetal doses were used for risk characterization of adverse developmental effects. • Section 4.5 of the draft risk evaluation is not clear on whether fetal endpoints are referenced to fetal or maternal doses. Section 4.3.5 (NMP Risk Evaluation, p. 277, lines 6474-6476) indicates that there was a lack of significant changes in maternal body weight for the corresponding decreases in observed fetal and pup body weights. These data support the concept that the fetal dose may be more appropriate for fetal endpoints than maternal dose, thus buttressing the use of fetal AUC and Cmax, as opposed to maternal values.	While fetal blood concentrations would provide the most accurate estimate of doses achieved at the target site, this type of information is rarely available for dose-response analysis. Dose-response relationships in developmental studies are often based on maternal oral or inhalation doses with no information about internal doses. For the NMP risk evaluation, PBPK models allow EPA to evaluate exposure, hazard, and risk in terms of internal doses. The PBPK model does not model fetal blood concentrations. EPA assumes that the average concentration reaching the fetus will be proportional to maternal exposure and used maternal blood concentrations as the metric to evaluate dose-response relationships in developmental exposure studies. EPA has

		slightly revised Sections 3.2.5.2 and 3.2.5.6 to further clarify this point.
Acute POD – Endpoint selection and dose-response analysis		
SACC, 57	**SACC COMMENTS:** • Recommendation: Discuss why fetal mortality/resorption was chosen as the critical endpoint when several endpoints, including reduced body weight and reduced perinatal survival, were affected at similar exposure concentrations. • Most of the Committee concluded that fetal mortality was an appropriate endpoint for evaluating acute exposure to NMP. It was noted, however, that several endpoints, including reduced body weight and reduced perinatal survival were affected at similar exposure concentrations. The Committee did not understand why resorption was chosen over these other measurements. **PUBLIC COMMENTS:** • EPA's default assumption that developmental effects could arise as a result of a single exposure (*i.e.*, duration equivalence of 15- and 1-day exposures) is a conservative one. The NMP dose for a single-day exposure is predicted to be approximately 2.3-fold higher than that for a 15-day exposure to yield an equivalent rate of fetal resorptions. Based upon this consideration, EPA's acute POD value of 214 mg/L based on 15-day exposures should be adjusted to a value that is 2.3-fold higher (492 mg/L) for a single-day exposure.	In the revised risk evaluation, EPA used "post-implantation loss" (combining resorptions and fetal mortality) as the critical endpoint for acute exposures. Resorptions are generally considered to be appropriate endpoints for evaluation of acute effects while other endpoints such as reduced fetal body weight are generally considered to be more appropriate for evaluating risks from repeated exposures. As discussed in the risk evaluation, "Resorptions can occur following a single exposure during a sensitive developmental stage and as such, resorptions and fetal mortality are considered a relevant endpoint for acute effects (van Raaij et al., 2003)." This was demonstrated in an analysis that compared the potency (NOAELs and LOAELs) of developmental toxicity reported in repeated dose studies and single dose studies (van Raaij et al., 2003). Van Raaij et al. found that there is a relatively small difference between repeated and single dose studies in the NOAELs and LOAELs reported for embryonic and fetal resorptions. While the difference in potency of single and repeated doses varied across chemicals, for some chemicals the potencies of single and repeated doses were equal. The study authors concluded that "resorptions observed in standard guideline-based developmental toxicity studies are considered to be relevant endpoints for setting limits for acute exposure." In contrast, while reduced fetal body weight is a sensitive endpoint that is considered a marker for fetal growth restriction which is often assumed to be representative of repeated dose rather than acute exposures (van Raaij et al., 2003).

		EPA also considered postnatal survival as a potential candidate for acute risk characterization but concluded that this outcome was not consistently observed across studies and when increased post-natal mortality was observed, the NOAELs were within the same range as other sensitive endpoints, such as reduced fetal body weight. Additionally, postnatal deaths occurred following multiple in utero and postnatal exposures, thus these outcomes were less likely to have resulted from a single developmental insult.
54, 32, 57	**PUBLIC COMMENTS:** • Considerable uncertainties are associated with derivation of risk estimates based on fetal resorptions and could be better analyzed and documented. • Importantly, there are NMP-specific data in Schmidt (1976) for which the issue of exposure duration can be addressed. This study assessed the effect of multiple exposure periods for mice exposed to NMP via intraperitoneal injection.	Schmidt (1976) demonstrates a 2- to 3-fold increase in post-implantation loss, as compared to untreated controls, following a single 166 mg/kg i.p. injection of NMP in mice on GD 7, 9, or 11. This supports the acute developmental toxicity of NMP, and it is consistent with the premise that a single-dose of NMP could result in embryo/fetal death. The effect and potency of a single exposure is likely to vary across specific days in development. As the Schmidt (1976) paper does not test the potency of single doses at every potentially critical period of gestation, it does not provide sufficient evidence to conclude that there are no specific periods of gestation during which a single exposure could be as potent as repeated dose exposures. The Schmidt (1976) paper does however provide additional evidence that the difference in potency between single doses and repeated doses of NMP is relatively small. This is consistent with the finding of the Van Raaij analysis described above. EPA assumed that single exposures to NMP could be as potent as repeated dose exposures during critical periods of development. The uncertainties and assumptions made around selection of post-implantation loss as an acute endpoint are described in Section 3.2.5.1.
SACC	**SACC COMMENTS:**	In the final risk evaluation, EPA used "post-implantation loss" as the critical health effect for acute exposures. This

	• Recommendation: Distinguish between embryonic resorption and fetal mortality in tables and text throughout the draft risk evaluation. • Fetal mortality and fetal resorption are two different endpoints but are considered as one in the draft risk evaluation, with confusion evident in both tables and text.	endpoint integrates early embryonic loss and fetal mortality in a single endpoint. In the developmental toxicity study protocols that evaluate these outcomes, biomarkers of embryo/fetal death (*e.g.*, empty implantation sites, or early and late resorptions) encompass both embryo and fetal developmental stages. EPA selected this combined endpoint because it can be modeled as a dichotomous endpoint. In addition, both stages of pregnancy loss are reported in several studies following NMP exposure. Considering embryonic resorptions and fetal mortality independently could underestimate the total impact of NMP on offspring survival through gestation.
SACC, 57	**SACC COMMENTS:** • Recommendation: Verify that fetal mortality data have been analyzed on a per-litter basis, re-analyze appropriately otherwise, and if this is not possible, discuss the reasoning for making conclusions based on fetal mortality data that are not litter adjusted. **PUBLIC COMMENTS:** • Dichotomous data for developmental toxicity studies are best assessed using a nested BMD model to account for potential litter effects (*i.e.*, effects that are not randomly distributed across litters); however, this would require access to the raw study data, which to date are not available.	In the final risk evaluation, EPA modeled post-implantation losses (including both resorptions and fetal mortality) based on reported mean losses per litter. As stated in the revised BMD modeling supplemental file: "To perform this analysis incidence of post-implantation loss from the reported litter means were modeled with BMDS standard dichotomous models after adjusting for litter effects using a Rao-Scott transformation. Normally, individual animal data are necessary in order to account for intralitter correlation present in nested developmental toxicity data (*i.e.*, the observation that pups from one litter are more likely to respond alike one another compared to pups from another litter). In this situation, study authors were unable to provide litter level data and instead an approximate approach was used. Briefly, the numbers of total implantations and total fetal mortality (dead fetuses plus resorptions) were scaled by a design effect in order to approximate the true variance of the clustered data. This transformation is called the Rao-Scott transformation and has been shown to reasonably approximate the variance due to clustering and intralitter correlation in developmental toxicity data (Fox et al., 2016)."

SACC	**SACC COMMENTS:** • One Committee member recommended that the study by Bartsch et al. (1976) that reports on acute toxicity in rats and mice to a range of solvents should be included in this discussion as it adds to the WOE and may address uncertainties.	Bartsch et al. (1976) reported LD50s for a range of solvents following acute exposures in rats and mice. The risk evaluation cites a range of LD50s in rodents across different endpoints (including LD50 data from Bartsch (1976) in the discussion of acute toxicity in Section 3.2.3.1. The acute POD selection is based on much more sensitive acute developmental endpoints, which were reported at doses well below the LD50s reported in the reasonably available data.
Chronic POD - Transparency of data		
SACC, 33, 54	**SACC COMMENTS:** • The Committee discussed reproductive toxicity in terms of male and female fertility and found it difficult to come to any conclusions given the complexity, and sometimes lack of transparency, in the data and analysis provided in the Exxon (1991) study. It was noted that the draft risk evaluation disagreed with the conclusions of the study regarding male and female fertility effects. • It should be noted that methods and data from all of the NMP Producers Group 1999 study (both rat and mouse experiments), which also examined reproductive endpoints, were also not available to the Committee for this risk evaluation. **PUBLIC COMMENTS:** • EPA indicated that the NMP reproductive studies were not included because they did not have access to the study reports. It is speculated that EPA made an unnecessarily restrictive and interpretation of TSCA Section 14.	EPA's independent analysis of the data in the Exxon 1991 study identified statistically and biologically significant effects on fertility in both males and females at all doses tested. While the study authors describe the effect as close to the range of historical controls, EPA concluded that concurrent controls in the study are the more appropriate basis for comparison. The NMP Producers Group 1999 studies were not shared with the committee because they were not available to EPA at the time of the meeting. In the draft risk evaluation, EPA discussed the evidence presented in summaries of the studies but was unable to evaluate study quality and did not rely on quantitative dose-response information from the studies. EPA has subsequently obtained access to the full studies. EPA evaluated the studies using the systematic review data quality criteria, performed dose-response analysis for developmental endpoints reported in the studies, and incorporated results of the studies into hazard identification, weight of the scientific evidence and dose-response analysis.
Chronic POD - Critiques of the Exxon (1991) key study		
SACC, 60, 33, 57, 33	**SACC COMMENTS:** • The Committee members noted that controls for the contemporaneous experiments are typically the better	The Exxon 1991 study was inadvertently not made available to SACC members prior to the peer review meeting. However, it had been shared with SACC members before the second day of the meeting.

	comparison group unless contemporaneous control level are at the extreme ends of the historical control distribution. The data used in these analyses are not available; hence, neither EPA nor the Committee were able to examine contemporaneous or historical control distributions, nor validate that conclusions were derived from correct statistical tests. **PUBLIC COMMENTS:** • Exxon (1991) should not be considered a high-quality study and should not be the basis for EPA's human health risk assessment. • The international regulatory authorities rated the Exxon study (reliability score of 2) inferior in quality to those conducted by the NMP Producers Group (reliability scores of 1) (OECD, 2007). • Exxon (1991) failed to adjust the concentrations of NMP in feed to reflect changes in food consumption that occur during pregnancy and lactation. • Other issues include increased probability of brother:sister matings, fertility problems at the specific Charles River site, reduction of females available for mating at the start of the P2 generation, and mating confirmation missed by laboratory personnel within the fertility and fecundity indices. • The reproductive effects noted in the Exxon (1991) study are likely related to the sensitivity of the testing strain's particular breeding background and the use of the 500 mg/kg/day dose level for the breedings to produce the F1b, F2a, and F2b litters. It is believed that the animals tested in the Huntingdon (1999) and BASF (1999) studies more accurately represent the true sensitivity of rats to NMP-related effects on fertility/fecundity.	EPA's independent analysis of the data in the Exxon 1991 study identified statistically and biologically significant effects on fertility in both males and females at all doses tested. While the study authors describe the effect as close to the range of historical controls, EPA, in agreement with this SACC comment, concluded that concurrent controls in the study are the more appropriate basis for comparison. Based upon the study report submitted to EPA, the Exxon (1991) study was rated high-quality by EPA. Study quality ratings from other organizations lack transparency and thus may not be particularly informative. 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. For example, NMP Producers Group submitted a report by Dr. Willem Faber which concluded that the Huntingdon (1999) and BASF (1999) (*i.e.*, the two NMP Producers Group studies) "more accurately represent the true sensitivity of rats to NMP-related effects on fertility/fecundity." This conclusion was based on Dr. Faber's review of the Exxon (1991) study, as well as on the conclusions of two additional documents pertaining to that study, *i.e.*, 1) a report of a "Good Laboratory Practices Audit" of the Exxon (1991) study written by an independent consultant, Linda Calisti, dated 22-Feb-2001 and 2) a review of the Exxon (1991) study (and other related correspondence) by Dr. Mildred Christian (Argus International, Inc.) dated 22-Jul-1999. The report by L. Calisti concluded that the Exxon (1991) report should be classified as non-GLP; however, the study report states that the study had been conducted under FDA GLP regulations, and the audit was conducted after the study data records had already been destroyed. Although the audit identified a

	• For fertility and fecundity, EPA should consider placing the data of Exxon (1991) within the context of data collected from other reproductive toxicity studies (NMP Producers Group, 1999a, 1999b; Solomon et al., 1995). EPA should consider all of the fertility and fecundity data within an overall data quality context.	number of procedural and record-keeping errors, they did not appear to invalidate the study GLP status or invalidate the study findings. The report by Dr. Christian agreed in principle with information submitted to California EPA (OEHHA) and concluded that EPA did not have sufficient information to identify the 500 mg/kg/day dose of NMP as toxic to reproduction. This conclusion was based on an assumption that the Exxon (1991) study rats might have been carriers of genetically-mediated testicular abnormalities and decreased fertility known to occur in some Charles River rats and to be sporadically expressed. The report indicates that this genetic anomaly was identified in the Charles River Laboratory Raleigh Production Room 1, the Raleigh Facility Room R10, and the Kingston Facility Room K83. However, according to the GLP audit by L. Calisti, the source of the Exxon study animals was the Kingston Facility Area K97. Thus, there is no evidence that the Exxon (1991) study animals were carriers of this genetic variant; it is merely speculative. Additionally, regarding the conclusion that the NMP Producers Group studies "more accurately represent the true sensitivity of rats to NMP-related effects on fertility/fecundity": first, 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. Secondly, 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 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 US, 9% of men aged

		25-44 years of age reported consulting a physician on infertility issues during their lifetime (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.
Chronic POD - Endpoint selection		
33	**PUBLIC COMMENTS:** • An assumption of early-life susceptibility for this endpoint is inconsistent with the exposure scenarios to which the assessment is applied. EPA should adopt a different endpoint that is applicable to adult worker exposures (*e.g.,* effects on fetal/pup body weight) or revisit the assumption of early-life susceptibility for the assessment of fertility effects.	EPA selected a chronic POD based on reduced male fertility and female fecundity in rats following exposures throughout gestation, lactation, development, and prior to mating. Relying solely on the available studies, and without additional targeted testing, there is no way to determine which periods of exposure contributed most to this effect. EPA assumes that this endpoint may be relevant for sensitive phases of human reproductive development, including pubertal development that may be ongoing in young workers. This POD is also assumed to be protective of other endpoints for which data are not reasonably available but which may be relevant to workers.
Areas that lack clarity		
SACC	**SACC COMMENTS:** • There is a lack of clarity on how the draft risk evaluation discriminates between positive vs. negative results. For example, Table 3-8 (NMP risk evaluation, pp. 187-8) shows positive, negative, and N/A results for effects of NMP exposures on various developmental endpoints. How these results factor into the overall WOE is not clear since the draft risk evaluation does not provide	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 could influence outcome are also important contributors to study outcomes.

	weights for individual health outcomes examined in each study. The risk evaluation could discuss the statistical power associated with the test for each study/outcome as one way of indicating which results are less likely to be a false negative or false positive. • Suggestions: o Consider providing a rationale for selecting the most applicable toxic endpoint for the assessment that is based on the available science, not simply choosing the most sensitive, especially when it is not corroborative with other data from other studies. o 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.	In selecting endpoints as the basis for PODs, EPA qualitatively considers the weight of the scientific evidence for specific outcomes of interest based on the quality of the studies, consistency of effects, relevance of effects for human health, coherence of the spectrum of reproductive and developmental effects observed and biological plausibility of the observed effects. EPA did not simply select the most sensitive study to be the basis for the POD. As described in Section 3.2.5.1, 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. EPA did not put greater weight on studies from specific exposure pathways. The PBPK model facilitates evaluation NMP toxicity based on internal blood concentrations regardless of exposure pathway. While the conditions of inhalation studies may be more relevant to human exposures than oral studies, they introduce more uncertainties around the level of exposure achieved. Whole body inhalation exposures may result in simultaneous oral exposures due to grooming behavior, resulting in a potential underestimate of total dose achieved. In addition, due to the hygroscopic nature of NMP, condensation reported in whole body inhalation studies may decrease the level of exposure to NMP achieved through inhalation while simultaneously increasing the amount of oral exposure to NMP following deposition on fur. For these reasons, oral exposure studies provide more reliable

		dose-response information, though exposure conditions are less directly relevant to human exposures.
SACC	**SACC COMMENTS:** • Recommendation: Specify which reproductive effect is particularly sensitive and consistent between studies. • In the draft risk evaluation (p. 178, lines 4371-74), the following sentence is unclear and confusing as written: "While reproductive effects are less consistently reported across studies than developmental effects, reduced fertility following exposure throughout gestation, lactation, growth, puberty, and prior to mating is a particularly sensitive endpoint."	EPA has revised the paragraph referenced by reviewers for clarity: "Several studies are available to assess the reproductive effects of NMP exposure. Reproductive effects are less consistently reported across studies than developmental effects, but significant reductions in fertility were reported in three studies. The reduced male fertility and female fecundity observed in the second generation of the Exxon study (1991) are particularly sensitive endpoints. These significant reductions in male fertility and female fecundity occurred in the second generation following exposure throughout gestation, lactation, growth, puberty, and prior to mating. Other studies with shorter exposure periods limited to the weeks prior to mating, also reported reduced fertility in male and female rats (Sitarek et al., 2012; Sitarek and Stetkiewicz, 2008), although NOAELs in these studies were higher than the LOAEL for reproductive effects identified in the Exxon study."
Other		
SACC	**SACC COMMENTS:** • Recommendation: Include air odor thresholds for NMP and note that it also has poor chemosensory warning properties. • One Committee member recommended that the risk evaluation include and discuss the fact that the air odor thresholds recommended for NMP at 4 ppm low to 10 ppm high are significantly above the 1 ppm PEL.	EPA has inserted the reported air odor thresholds for NMP for reference. OSHA has not established a PEL for NMP. The California PEL of 1ppm does not serve as the basis for any of EPA's risk conclusions in this risk evaluation.

6. Dose-Response Assessments

Dose-Response Assessments		
Charge Question 5.1: Please comment on EPA's use of the PBPK model used to derive internal dose estimates (Poet et al. 2010, 2016). Please comment on whether the model is clearly and transparently described and technically and scientifically adequate for supporting the NMP draft risk evaluation. Specifically, please address the structure of the PBPK model, parameter calibration and model predictions of the available in vivo data. Please comment on the dose metrics selected for acute (Cmax) and chronic (AUC) PODs. **Charge Question 5.2:** Please comment on the BMD analysis conducted on the endpoints identified from the key studies. Please specify whether the BMD calculations were appropriately conducted and documented and whether the BMRs applied for each endpoint are appropriate.		
#	**Summary of Comments for Specific Issues Related to Charge Question 5**	**EPA Response**
PBPK modeling – Model transparency		
SACC	**SACC COMMENTS:** • Recommendations: Describe which version of the PBPK model was used, and clearly describe modifications made to the model since it was published. Articulate clearly the meaning of "peer-reviewed" with respect to the PBPK model used. • The Committee was unable to determine whether the EPA 2015 peer review of the Poet PBPK models reviewed the same models used in the draft risk evaluation. Appendix I indicates that the PBPK models had experienced extensive revisions since the 2015 review and might be considered a new model. Any PBPK model employed in an evaluation should have a recent complete peer review. The description of the PBPK model as "peer reviewed" could be misleading.	EPA's PBPK model is based on a model that was published in the peer-reviewed literature by Poet et al (2010). EPA modified the model for use in the 2015 risk assessment. There are some differences between EPA's model and the 2016 model published by Poet et al. Appendix I (now Appendix J) describes the EPA PBPK model used for this risk evaluation. The Appendix has been revised to include a more complete description of all parameters used in the model and all modifications made to the model since the Poet et al 2010 publication. While there are differences in the details, the model is in most aspects that which has been described in the peer review literature by Poet et al. (2010). The model went through additional review as part of EPA's 2015 risk assessment of NMP.
SACC, 56, 33, 31, 54	**SACC COMMENTS:** • Recommendation: The final PBPK model code and model parameters used in assessing each scenario	EPA shared the PBPK model code publicly immediately following the peer review meeting. The model itself has not been substantively changed since the 2015 risk assessment;

	should be fully described and made available for external peer review (*i.e.*, PBPK model code files should be provided in the docket as part of the supplemental materials for the NMP draft risk evaluation in a form that would allow the informed/scientific/modeling public to review and run to validate findings). • There was concern that the PBPK model used had been modified since the EPA 2015 review and a full review of the final code used had not been performed. Without the final code, validation by members of the Committee was not possible. The complete and documented PBPK model code used in the draft risk evaluation was not available to the Committee for its experts to fully review. Code is shown for various aspects of the model but not for all components and not in a systematic manner. **PUBLIC COMMENTS:** • Access to the full code, the model input parameters, and tabular outputs are requested. • Other information needed includes weight fraction in the liquid product, skin surface area, GPF, dermal exposure duration, air concentration, and worker body weight.	only model inputs have been modified. A summary of model parameters, corrections made since the 2010 model and additional minor corrections made in response to this public comment process are described in the revised model code and Appendix J. Scenario-specific exposure model inputs (including weight fraction, body weights, exposure duration, skin surface area, etc), PBPK exposure estimates and risk calculations are all included in the occupational exposure and consumer exposure supplemental excel files.
SACC, 54	**SACC COMMENTS:** • Recommendation: Explain and clarify the structure of the PBPK model as used to derive internal doses of NMP in this risk evaluation. Some on the Committee remarked that the information provided in the draft risk evaluation (Appendix I) is insufficient to fully document the modeling approach used (for example, no diagram is provided describing the rat or human	To increase transparency of the model, EPA has expanded its discussion of the PBPK model in Appendix I (now Appendix J). EPA inserted a figure outlining the structure of the rat and human PBPK models (as described by Poet et al (2010) and added tables summarizing all partition coefficients and parameters used in the model. Appendix J also documents optimization of specific

	PBPK model structure, with all tissue compartments described, etc.). **PUBLIC COMMENTS:** • EPA should expand its discussion of this specific PBPK modeling exercise, including its overall objective and any conclusions that can be drawn based on the calculated applied doses across candidate studies.	parameters that was performed based on data from available studies, including a discussion of the purpose and conclusions of these parameter optimization exercises.
SACC	**SACC COMMENTS:** • Recommendation: Poet et al. (2016) should be referenced in the risk evaluation and details of the two human dermal studies clearly described in the risk evaluation. • An inhalation study in adult humans was used in the draft risk evaluation (Bader and Vanthriel, 2006). The description seems to differ from what was reported in Poet et al. (2016). In the study, dermal penetration was estimated for volunteers wearing shorts and tee shirts and volunteers breathed filtered air, so there was no exposure to the vapor. Details about the clothing worn by the inhalation group in the other study are missing and should be provided.	As described above, the PBPK model was modified from the Poet (2010) publication for use in the 2015 risk assessment. Since then, some additional modifications have been made in response to public comment. Poet et al (2016) is not cited in the risk evaluation because it is not consistent with the PBPK model used by EPA. Several parameters differ in the two versions of the model. Appendix J is the appropriate reference for details of the PBPK model. To increase model transparency, the appendix has been modified to provide additional details of the PBPK model structure and parameters. As provided for the Akesson dermal study, details about clothing worn in the Bader and Van Thriel inhalation study are included in Appendix J: "Volunteers wore slacks and T shirts and thus had arms exposed to vapor."
SACC, 54	**SACC COMMENTS:** • Recommendation: Describe and tabulate the settings for PBPK model internal parameters used for each condition of use scenario and make available in a supplemental document. • Values for internal parameters (body weight, volumes of tissues, respiration rate, flow rates through and among tissues, and other physiological rate parameters, etc.) used to model the internal dose metrics were not readily available. These are critical to understanding	The standard input parameters and partition coefficients used in the PBPK model are now summarized in tables in Appendix J. The input parameters that are exposure-scenario specific can be found in the supplemental occupational and consumer risk calculator excel files. The risk calculator files contain all scenario-specific PBPK model inputs as well as the PBPK outputs (*i.e.*, exposure levels predicted by the PBPK model) and the final risk calculations based on those predicted exposures. EPA's PBPK model code is publicly available on the EPA website.

	the adequacy of the PBPK model in occupational settings. **PUBLIC COMMENTS:** • EPA should also provide an example calculation with selected model inputs and provide a citation to the exact location of the PBPK files where the code and output specifically for the applied dose calculations are located.	
PBPK modeling – Assumptions, uncertainties, and sensitivity analysis		
SACC, 54	**SACC COMMENTS:** • Recommendation: Explicitly state assumptions and uncertainties associated with use of the physiologically based pharmacokinetic (PBPK) model to estimate internal dose metrics, particularly route-to-route extrapolation. Provide estimates of the magnitude of influence of each assumption on the final estimate of the POD. • PBPK model calibration represents multi-variable fitting, which can result in apparently good fits without being physiologically logical or "correct." This uncertainty is not discussed in the draft risk evaluation. • One Committee member suggested that assumptions used to construct the model, and uncertainties in the model's parameterization, might affect the PODs. • The Committee agreed there should be more information provided on the model and on how central and high-end tendencies were derived. **PUBLIC COMMENTS:** • EPA should provide additional discussion of uncertainties and consider providing sensitivity analyses using alternative PBPK parameters.	EPA has inserted additional discussion of the assumptions and sources of uncertainty related to the PBPK models used to derive PODs from animal data and to estimate human exposures for each COU in Section 4. To the extent possible, EPA describes the potential magnitude of each source of uncertainty. For several sources of uncertainty, EPA lacks the quantitative information that would be necessary to characterize uncertainty for some parameters. For many human exposure scenarios, EPA relies on assumptions about specific exposure parameters for which there is a lack of reliable data. Where plausible alternate assumptions have been proposed by stakeholders, EPA has considered 'what if' scenarios, estimating exposure based on several alternate assumptions. These alternate exposure estimates provide an indication of the magnitude of uncertainty associated with EPA's assumptions. EPA believes that the qualitative and quantitative analyses included in the risk evaluation provide sufficient information to support risk conclusions. A comprehensive quantitative uncertainty analysis for all parameters used in the rat and human PBPK models would require substantial additional analysis that is beyond the current capacity of the agency within the time available for completion of risk evaluation. For example, one source of

		uncertainty is that the model only uses a single compartment to describe the skin vs. multiple skin layers or a partial differential equation. EPA is not able to quantify the uncertainty from this assumption without building the more elaborate model forms, calibrating new parameters and/or re-fitting new ones, and seeing how that impacts model results.
PBPK modeling – General model design and assumptions		
SACC	**SACC COMMENTS:** • Recommendation: Verify that there is no concern for buildup of NMP during prolonged/repeated exposures by applying the PBPK model to an appropriately selected scenario. • A Committee member indicated that more support is needed for the statement made in footnote 1 of Table 4-3 (NMP Risk Evaluation, p. 212), which states: "It is assumed that there is no substantial buildup of NMP in the body between exposure events due to NMP's short biological half-life (~2.5 hrs.)" Support for this statement can be provided by applying the PBPK model to a suitable scenario (*e.g.*, one that would be expected to show build up, such as from long exposures at high concentrations). • The meaning of the phrase "substantial buildup" in this context needs definition.	To provide a quantitative basis for the assertion that there is a lack of "substantial buildup", EPA has added additional analysis demonstrating that there is no buildup of NMP week to week. For workplace exposures, seven days are simulated, with the first five being exposure days, and average or peak concentration is calculated over this time. Simulations were performed starting on either day 0 or at 8 months of pregnancy to assure that the largest internal dose that might occur from a work week during pregnancy is calculated, but the difference between those two points of pregnancy was minimal. As is shown by the example plots now included in Appendix J, the blood concentration returns essentially to zero by the end of the 7th day; *i.e.*, after 2 (weekend) days without exposure, even for the highest exposure scenario. For evaluation of consumer exposures, it is assumed that these are single-day exposures associated with home projects that are not performed repeatedly over multiple days. So, accumulation cannot occur for such scenarios.
SACC	**SACC COMMENTS:** • Recommendations: Justify running the PBPK model for the first day or week of pregnancy instead of for the entire pregnancy. • The text states that the PBPK model was run for the first day or week of pregnancy when physiological changes are minimal; however, the point of using a pregnancy model is to be able to predict dose metrics	For rat developmental studies, simulations were run for the entire portion of pregnancy during which exposure occurred and peak and average blood concentrations were calculated. When calibrating the model against human PK collected from non-pregnant adults, it is appropriate to use simulations when there are minimal changes vs. later in pregnancy. For human pregnancy, simulations were run to estimate the internal doses at several points in time during pregnancy, from

	for the entire pregnancy to capture the impact of the physiological changes during pregnancy. This requires more computational time, but it should be done even if only for one case to demonstrate that EPA's assumptions would result in the most conservative estimate.	beginning to end. It was found that the highest internal dose was predicted for early pregnancy because respiration rate increases as BW0.75 and dermal contact is assumed to be constant, while BW increases, indicating that internal dose/BW decreases as pregnancy progresses. Therefore, the early pregnancy simulations provide the most health-protective estimates.
SACC	**SACC COMMENTS:** • Recommendation: Describe the process used to develop the pregnant human female PBPK model and how it was used along with the pregnant female rat PBPK model to inform chronic toxicity endpoints. • It appears that no data informing processes in pregnant human females were used in developing the pregnant human female PBPK model. The approach used was not clearly described. • One Committee member explained that, during pregnancy, induced enzyme activities in humans could be variable and increase up to 30%. It was unclear to the Committee the extent to which the PBPK model accounts for induced enzyme activity and if it does, the extent to which this source of variability is accounted for. This needs clarification.	The PBPK models for pregnancy accounted for pregnancy-related changes in blood flow, respiration and body weight. Changes in enzyme activity that occur during pregnancy are not captured in the PBPK model. There is evidence that Cytochrome P450 2E1 (CYP2E1) contributes to NMP metabolism (Ligocka et al., 2003) and that CYP2E1 expression decreases during pregnancy in rats and mice, but there is insufficient information about the overall impact of these changes on NMP metabolism. There is also insufficient information about other metabolic pathways that contribute to metabolism and how they may change during pregnancy. EPA concluded that there is not sufficient quantitative information about pregnancy-related changes in NMP metabolism to incorporate this into the model. In the absence of more quantitative information, EPA assumed the interindividual uncertainty factor of 10 (with a factor of 3 designated for toxicokinetic differences across individuals) is sufficient for addressing metabolic differences associated with pregnancy.
SACC	**SACC COMMENTS:** • Recommendation: Demonstrate that modeling a single exposure on each day of gestation is comparable to running repeated dosing and computing the average AUC. • If the repeated exposures are going to be used to calculate internal dose metrics that are then used to assess acute exposure, then modeling a single exposure	As described above, for workplace exposures, seven days are simulated, with the first five being exposure days, and average or peak concentration is calculated over this time. Simulations were performed starting on either day 0 or at 8 months of pregnancy to assure that the largest internal dose that might occur from a work week during pregnancy is calculated, but the difference between those two points of pregnancy was minimal. As is shown by the example plots now included in

	on each day of gestation must be demonstrated to be comparable to running repeated dosing and computing the average AUC. To this end, it could be useful to have a table comparing the single dose and repeated dose studies mentioned in the draft risk evaluation (p. 195, Section 3.2.5.1, lines 4547-4553) that were used to justify this approach.	Appendix J, the blood concentration returns essentially to zero by the end of the 7th day; *i.e.*, after 2 (weekend) days without exposure, even for the highest exposure scenario. This demonstrates the buildup is not expected from repeated dose exposures during pregnancy.
SACC	**SACC COMMENTS:** • Recommendation: Explain how the co-exposure of NMP with 2-pyrrolidinone impacts the pharmacokinetics of NMP. • The oral data used for calibration of the rat model was for NMP co-exposure with 2-pyrrolidinone. There is no discussion in the publication's supplemental material as to how the co-exposure could have affected the pharmacokinetics of NMP. These same data were used to justify the addition of dual absorption. While the authors also cite other publications to support this modification, it is unclear if any of these publications are NMP-specific. • Clarify how oral data by Midgley et al. (1992) used to fit a 2-compartment stomach in a study that co-administered NMP with another chemical, 2-pyrrolidinone, was acceptable for describing the absorption pharmacokinetics of NMP.	Since absorption of NMP is not known to be transporter-mediated (*i.e.*, occurs by simple chemical diffusion) it is unlikely that the presence of 2-pyrrolidinone would have an effect. Further, the same absorption rate constant adequately fits the Ghantous data from female rats, though it over-predicts the Ghantous male rat data, which were obtained with no co-exposure. If anything, the co-exposure would be predicted to reduce absorption though some form of competition. Thus, in combination with these other data, there is no indication that absorption is under-predicted (which would lead to an under-prediction of risk). With the focus of the assessment being on developmental risk, the fact that the male rats in the Ghantous study appeared to absorb NMP more slowly than the females is not a significant issue.
SACC	**SACC COMMENTS:** • Recommendation: Comment on the impact of not including dermal uptake of NMP vapors or oral uptake of NMP during grooming on the internal doses in the rat PBPK model and how this impacts the estimates of and associated confidence in the final POD value. • Air exposures in the PBPK model were parameterized based on a nose-only exposure study (Ghantous, 1995),	Separate model code was developed for rats vs. humans. The rat code was not changed to include vapor-through skin absorption. Vapor-dermal uptake and grooming were not included, but it is presumed that these contribute little to overall uptake (< 20%). Because those routes are not included, the estimated inhalation dose from inhalation studies in rats could under-predict the total exposure levels that result in reproductive toxicity effects in animal. While this source of

	and then used to predict whole-body exposures described in Saillenfait et al. (2002; 2003). Therefore, in rats, model predictions for whole-body exposures for developmental toxicity studies do not include any contributions from dermal uptake of vapors or oral uptake via grooming. Estimated internal doses could be lower than the actual internal doses in these studies, resulting in an underestimate of the POD.	uncertainty could result in an underestimate of the dose at the POD, this would not contribute to an underestimate of risk because the primary studies used for quantitative analyses for the PODs following acute and chronic exposures would not be impacted by this source of uncertainty.
SACC	**SACC COMMENTS:** • The PBPK model models skin as a Continuously Stirred Tank Reactor (CSTR). Traditionally, experimental permeation data are evaluated using mathematics representing steady state diffusive flux through a membrane. Diffusive transport in a membrane and loading/release in a CSTR are fundamentally different. Matching of traditionally determined experimental permeability coefficients and permeability coefficients backfitted by PBPK modeling should not be expected or viewed as confirmatory.	While the U.S. EPA clearly will correct model features that are considered to be critically deficient, even if a model has been accepted for peer-reviewed publication, EPA does defer to the journal peer review process, particularly for aspects of a model that do not critically impact model predictions. This aspect of the model structure was clearly present in the model as originally described by Poet et al.(2010). The fit to the rat dermal exposure data of Payan et al. (2003) is adequate and is not critical since the rat bioassays were by oral or inhalation exposure. The fit to the human dermal PK data of Akesson et al. (2004) was also considered adequate. In particular, the peak concentration after exposure to neat or 50% NMP was not under-predicted, and while the initial rate of absorption from 50% NMP was somewhat over-predicted, the AUC from that exposure was not under-predicted. So, use of this model feature as accepted for the Poet et al. (2010) publication does not appear to under-predict human dosimetry and hence risk, and therefore it is appropriate for the EPA to defer to the journal peer review acceptance. The comment also implies that fitting of the permeability constant to the PK data as occurred for this model should not be acceptable. EPA respectfully disagrees, as it is typically the case that PBPK parameters are empirically fitted to observational data, as occurs for the oral absorption and metabolic elimination constants for this model. By analogy,

		inhalation uptake for some gases is less than predicted by the alveolar equilibration equation because a process referred to as "wash-in/wash-out" occurs in the upper respiratory tract and conducting airways. This effect is typically accounted for by empirically fitting an absorption fraction, since inclusion of a mechanistic model for absorption and desorption in the conducting airways would increase model complexity by a large extent and is presumed not to improve the overall model applicability for prediction of systemic dosimetry. Rejection of empirically fitted absorption constants would reduce the number of PBPK models considered acceptable for use, when these are otherwise the preferred means of estimating human dosimetry and is not viewed as an action that would significantly improve EPA's ability to accurately predict human risk.
SACC	**SACC COMMENTS:** • Permeability coefficients are vehicle specific. Permeability coefficients obtained from neat compound experiments (*e.g.*, Payan et al., 2003) should not be assumed to apply when NMP:water mixtures are used at varying NMP weight fractions (*e.g.*, see Marquet et al., 2015).	EPA appreciates this comment as distinct permeability values were estimated for neat vs. dilute NMP in humans but these were not applied consistently for all analyses. As noted in response to a previous comment, since most of the rat bioassays did not involve dermal exposure, the fact that rat dermal permeability was only measured with neat NMP is not an issue with regard to rat model application. Akesson et al. (2004) did measure dermal absorption in humans exposed to neat or 50% NMP and separate permeation constants were fit to each concentration. Although a wider range of concentrations wasn't tested, the decision on how best to use these results is described in response to a similar comment, below.
SACC	**SACC COMMENTS:** • There is a disparity between predicted dermal vapor uptake and the Bader et al. (2008) data. The impact of this disparity is unknown, meaning that it is uncertain whether the PBPK model over- or under-predicts the	As described in Section 3.2.5.5 of the risk evaluation, "The discrepancy between the Bader et al. (2008) data and the current model predictions could be because the subjects in Bader and van Thriel (2006), on which this model is based, wore long-sleeved shirts, thereby reducing dermal absorption

	dose metrics.	or due to the use of an idealized model of inhalation uptake which could over-predict uptake by that route." In the absence of scenario-specific information on clothing, EPA assumes that the surface area of skin exposed to vapor through skin is 25%, corresponding to the face, neck, arms and hands. While there is some uncertainty around the impact of that assumption, EPA makes scenario-specific adjustments to the surface area of skin exposed to vapor where EPA has information to indicate that workers are more fully protected by PPE.
SACC	**SACC COMMENTS:** Recommendation: Modify the discussion in Appendix I on the PBPK models to address the issues identified by the Committee with the rat and human PBPK models listed below: a) Based on the figures in the Poet et al. (2016) publication, the rat model underpredicts the rate of the metabolite into the plasma for the higher dose and overpredicts it for the lower dose. This could have an impact on predicted dose metrics for NMP (*i.e.*, if the under- and overprediction of metabolite data is due to metabolism parameters). b) The rat model calculates changes in tissue volume for maternal fat, liver, uterus, and mammary tissue, but only adjusts blood flow to these tissues, based on the volume increases, for fat, uterus, and mammary tissue. There is no explanation of why the liver blood flow is not adjusted. This may have been an oversight and could affect dose metric predictions. **c)** In the rat model, urinary excretion is subtracted from the arterial blood compartment equation but the equation for urinary excretion uses a volume for venous blood. In the submodel for the metabolite, this	Appendix J (previously Appendix I) has been updated to provide summary information about model structure and parameters. In response to specific points raised by the SACC: a) Dr. Poet was not in complete agreement with changes that the U.S. EPA made to her model and she implemented some additional changes and modified parameter values prior to the 2016 paper. While Dr. Paul Schlosser agreed to be a co-author on that paper, the U.S. EPA modeling does not use the parameters and fits shown by Poet et al. (2016), but those shown in the PBPK appendix for the assessment. In particular, EPA chose to focus the human model calibration on the low-concentration data, as these are considered most relevant to low-concentration exposures. As shown by the simulations vs. the human data, these parameter estimates are likely to over-predict human dosimetry and risk at higher exposures but should not substantially under-predict dose/risk. b) This is an oversight in the documentation. Liver blood flow is also increased in proportion to liver volume. c) We appreciate the SACC noting the error in the urinary excretion equation, but since the excretion constant (KLN) is fitted, it can be corrected without effecting the quantitative predictions. Defining KLNnew =

	is reversed with urinary excretion being subtracted from the venous blood compartment (using a total blood volume as there is no arterial blood compartment in the submodel) but using the arterial blood volume in the equation for urinary excretion. d) The rat model code in the Poet et al. (2016) publication had the model variable named DNN defined as a state variable (*i.e.*, the integration of a rate variable and then again with an arithmetic equation in a DISCRETE block). Appendix I describes some model changes made with regards to liquid dermal exposure and the parameter, DNN. It was not possible to verify that these changes were implemented correctly.; In the INITIAL section of the model the equation for DDNX is defined as ConcL*VLiq. In the DISCRETE block called REAP, it is defined as ConcL/VLiq*FAD. Given that this parameter is used in conjunction with DNN, this may have been corrected but the Committee cannot tell without EPA's code listing. **e)** The M script file included in the supplemental material for the 2016 publication indicated the parameter NumFet is set to 0.01. This parameter is described as the number of fetuses in the litter and setting NumFet to this value has an impact on several other equations such as maternal body weight. There is no explanation of why this is done or if it is changed for all runs conducted for this draft risk evaluation. f) The constant for VSkC, described as fractional skin volume, is set the same in the human model as it is set in the rat model (as found in the M scripts). While the Committee did not search the literature for fractional skin volumes for rats and humans, the value being the same for both seems unlikely.	KLN*VV/VA, then KLNnew*CA*VA = KLN*CA*VV. Since venous blood volume is assumed to be 75% of the total blood volume and arterial blood is 25%, setting KLNnew = 3*KLN and correcting the equation in the model results in identical predictions. These changes have been made. d) The U.S. EPA version of the model does not include variable DNN. EPA does apply the factor, FAD, to calculate a corrected liquid concentration (CONCL2 = CONCL*FAD), to account for < 100% absorption. CONCL2 is then used as the initial concentration in the mass balance for NMP in the liquid layer on top of the skin. e) Since the PK data used for rat model calibration were in non-pregnant animals, NUMFET = 0.01 for those simulations, to minimize the impact of the fetal compartment. (Setting NUMFET = 0 would lead to divide-by-zero errors.) For developmental bioassay simulations, NUMFET = 14. The EPA model workspace uses a 'ratparam.m' script to set default parameters for non-pregnant rats, including NUMFET = 0.01, and 'preg_ratparam.m' to set pregnancy-specific parameters for those simulations. f) For the rat VSKC is set to 0.19 in the initial block of the EPA model code and is not reset in the parameter scripts. For the human it is set to 0.051 in the 'human_params.m' script. These are the values as listed in Table 1 of Poet et al. (2010), cited from Brown et al. (1997). g) During the time when liquid is present on part of the human skin, it is reasonable to assume that vapor does not simultaneously contact that portion of the skin. It is assumed that if vapor is present in the air and PPE is not being worn, the exposed skin is otherwise exposed to

	g) How the human PBPK model defines the skin compartments for liquid and vapor exposure assumes that the two do not overlap. It is questionable how accurate a description this is for the actual exposures. h) The model defines the variable named DDN as (ConcL-1.0)*VLiq0*FAD. Appendix I states that this was done to avoid potential division by zero; however, it appears this could cause a larger issue by potentially running the model with a negative amount in liquid if ConcL is zero. There are better ways to avoid division by zero. i) The model defines QPlaI in the INITIAL section in terms of VPlaI before VPlaI is defined. The INITIAL section is not sorted when the model is compiled so when the model calculates QPlaI, it does not yet know the value for VPlaI and, therefore, will use a value of 5.55e+33. The value of QPlaI will be quite large at the first time point and may affect AUC and Cmax estimates. It was not mentioned in Appendix I in the modifications to the model that this was corrected. j) QSlw is calculated in the model code by subtracting QPlaI. The pregnancy code is reported to be based on Gentry et al. (2002), but that model does not subtract QPlaI from QSlw. k) PDose, PDose2, and PDose3 are labeled in the INITIAL section as being in units of mg/kg, but when ODose1, ODose2, and ODose3 are calculated by multiplying these by body weight (in kg) and FracOr (unitless), they are labeled as being in µmoles. Given the equations later in the model, ODose1, ODose2, and ODose3 should be labeled as being in mg. **l)** The SCHEDULE statement, IF (ON3) SCHEDULE OND3.AT.S3, uses the parameter ON3 as a logical	vapor. PPE is assumed to occlude the skin from vapor exposure when worn. It is possible that a portion of the skin which is assumed to be only exposed to vapor is actually exposed to liquid. This would be an error in the exposure assessment and model input parameters; *i.e.*, the area exposed to vapor should be reduced and the area exposed to liquid should be increased to reflect the actual exposure. But otherwise EPA believes it is reasonable to assume that a given cm2 of skin cannot be simultaneously exposed to vapor and liquid. Since the absorption from liquid far exceeds the absorption from vapor, the key factor is that liquid exposure should not be under-estimated. EPA believes that its estimation of liquid exposure area is reasonable. h) DDN: The multiplier FAD is used to force this term to zero outside of periods with explicit liquid-dermal exposure. With a density of 1.02x10^6 mg/L, the concentration in even a 10% solution is 5 orders of magnitude greater than 1. For none of the liquid-dermal exposure simulations conducted does the concentration even approach 1. So, for practical purposes this is a non-issue. While other means of avoiding divide-by-zero may exist, EPA believes that the equation as it exists is sufficient for the current model application. i) In the U.S. EPA human model code, VPlaI is defined on line 217 and QPlaI is defined on line 234. j) The change in the calculation of QSlw from the Gentry et al. (2002) model is described in the PBPK appendix section on "Tissue and Blood-Flow Mass Balances." This and other changes noted were made to provide balanced flow volumes. k) The U.S. EPA model code only uses PDOSE and ODOSE1. The comments on the same line as the equations

	variable. ON3 has not been declared as a logical variable and is defined with a value of 1.0. Logical variables must have an integer value of 1 or 0 or, in the CSL file with ".TRUE.", ".T.", ".FALSE." or ".F." The Committee is unable to tell if this was corrected in the models used, and this was not mentioned in the changes in Appendix I. m) The DISCRETE blocks named DOSE1, DOSE2, and DOSE3 use parameters TIME, TIME2, TIME3, and REPTM. While these parameters are set in the M script file, they are not set or defined as a constant in the model definition file. This could result in inaccurate predictions if the values are not set prior to running the model as the model does not have default values. n) The model is coded to start the simulation after pregnancy has started (*i.e.*, increases in tissues volumes calculated in INITIAL block as the non-pregnant fractional value plus an increase based on the point in the pregnancy at which the simulation is to start), and the initial body weight is set at the default pre-pregnancy weight. The body weight needs to be updated after these initial tissue volumes are calculated in the INITIAL section to account for these larger than pre-pregnant tissue compartments. Then in the DERIVATIVE section, the model currently adds the increase from the initial tissue volumes (*i.e.*, VFat-VFatI) to the initial body weight at the beginning of the simulation for fat, mammary tissue and uterus but not for fetal and placental weight. This needs to be corrected as the body weight (once modified as necessary in the INITIAL section) already includes a value for fetal and placental weight and only needs the additional increase included.	correctly identify it as having units of mg. A stray comment re. converting to µmole (presumed to be a legacy comment) has now been deleted. l) While ON3 has not been defined as a logical variable, examination of model simulation outputs shows that the scheduling statements have worked correctly, as the value is either set to 0 or 1 in various scripts. This can be seen in the plots of the Bader and van Thiel exposures (ON3 = 1) vs. Akesson and Paulsson (ON3=0). The .csl file has now been updated to declare it as a logical variable. But the reviewer is mistaken that one must use .TRUE., etc., in setting its value. Logical variables can also be set to 0 or 1 as the equivalent of FALSE and TRUE, respectively. Computer logic is ultimately performed using binary numbers, not symbols, and the use of .TRUE., etc., is simply a convenience introduced in acslX. m) The EPA version of the model does not use the DOSE1, etc., discrete blocks. n) Because the initial masses of the placenta and fetus (as defined by the model equations) are 6.8e-5 and 4.9e-9 kg, respectively, the error from not subtracting their initial values in the overall mass balance is minimal. Therefore, the model code has not been updated as suggested. o) RADVL, which is the rate of vapor absorption on areas of skin which are exposed to liquid during times when liquid isn't present, is another component of the EPA model with which Dr. Poet disagreed, hence does not appear in the code for the Poet et al. (2016) publication. It is defined on line 427 of EPA's file, HumPregRev2.clean.csl. The equations for RADL (absorption when liquid is present) and RADVL are as follows: RADL = (PVL*SAL/1000.0)*(CSURF - (CSKL/PSKL))*czone*BRUSH

	o) Appendix I mentions an equation for RADVL which is not in the code listing in the supplemental material for the 2016 publication. RADVL is mentioned in some comments in the model code but there is no equation. Without EPA's code listing, the Committee is unable to tell if this was added. p) PregTime is set in the M script file to 0.0001. This seems like an odd choice.	! Net rate of delivery to "L" skin from liquid, when liquid is there ADLL = integ(RADL, 0.0) RADVL = (PV*SAL/1000.0)*(CI - (CSKL/PSKA))*(1.0-Czone*BRUSH) ! Net rate of delivery to "L" skin from air, when liquid not present p) PregTime is not in the EPA model and the primary input time constant is GDStart, which is the day of gestation on which exposure simulation starts; it is either set to 0 or 240 days.
34	**PUBLIC COMMENTS:** • EPA should provide the blood:air partition coefficient; this is the key parameter that an inhalation toxicologist needs to understand respiratory tract absorption	The blood-air partition coefficient for NMP is 450. This is now included in the PBPK Appendix (Appendix J) in the risk evaluation.
54, 56	**PUBLIC COMMENTS:** • EPA should use dermal permeability constants in the PBPK model that accurately reflect the variability of skin thickness on the hand.	The comment is suggesting that the surface area of the skin be divided into sub-regions, each with its own thickness. Areas with greater thickness will have less absorption, areas with lower thickness will have greater absorption. Since absorption is proportional to the difference between concentration on the surface and concentration in blood, the result will be the same as using a single surface area with a weighted-average thickness, where the weighting is by the area of skin with each thickness. EPA is not aware of detailed information on the variation in skin thickness across the hands, data that would be required for such an elaboration of the model. If there are data to indicate that the average thickness of skin on the palms and under side fingers is different from that used in experiments from which the dermal penetration constant was measured (for example, that skin is on average one-half the thickness of skin on the upper arm), then the model could easily be adjusted to reflect this difference without sub-dividing the liquid-exposed

		skin compartment.
57, 33	**PUBLIC COMMENTS:** • The parameter values used in the PBPK model are overly conservative. EPA should consider using human parameter values that are appropriate for the concentration range of interest (*i.e.*, near the POD values), rather than those that were specifically optimized for low concentrations of NMP.	As described in Appendix J, the mechanism for nonlinearity of NMP concentrations in blood is unclear. EPA applied parameter values derived from low exposure levels in order to avoid creating a model that underestimates blood concentrations for low level exposures relevant to conditions of use considered in this risk evaluation.
57	**PUBLIC COMMENTS:** • Because future decisions made for NMP under TSCA are expected to be driven in part by the risks associated with high concentrations NMP in air, it is critical that the human PBPK model be appropriately parameterized for these exposure conditions. • EPA should either utilize all of the data from Bader and van Thriel (2006) to estimate a single set of parameters for describing NMP metabolism in humans or estimate two sets of metabolism parameters: one for low intensity exposures [<2.5 ppm, continuing to utilize the 2.5 ppm data from Bader and van Thriel (2006) alone], and another for high intensity exposures [>2.5 ppm, utilizing the 10 and 20 ppm data from Bader and van Thriel (2006)].	Considerable thought was put into why the human internal concentrations were relatively reduced at higher vs. lower concentrations from this study. Given the interval between exposures, metabolic induction did not seem likely. The other possibility was that the subjects were reducing their activity level and hence respiration at the higher exposures, perhaps because of the NMP odor. Without respiration data, such concentration-dependent behavior cannot be verified, and reduced respiration is not something that a person involved in physical labor would be able to achieve. Hence, EPA does not believe it appropriate to extrapolate this empirical concentration-dependence to predictions for workplace or residential user exposures; *i.e.*, in the absence of knowing the underlying mechanism. In the absence of such a correction, the over-prediction of internal doses for **some** of the Bader and van Thiel (2006) subjects is less than a factor of 3. To follow the suggestion exactly as given would lead to a discontinuity in the predicted internal dose between predictions for individuals exposed to 2.4 ppm and 2.6 ppm, for example, where the individual exposed to 2.6 ppm would be predicted to have a lower internal dose than the person exposed to 2.4 ppm. This is clearly unrealistic. A more realistic approach would be to determine Vmax as a function of exposure concentration (or blood or liver concentration) such that there is a continuous, increasing relationship between

		exposure and internal dose. But such a model would require scientific review. Since the current model is health-protective (does not under-predict internal dosimetry) and the suggested revision is beyond the scope of the current assessment, EPA will consider such a revision in the future.
PBPK modeling – Application of the PBPK model to estimate rat exposures in key studies		
SACC, 57, 33, 54	**SACC COMMENTS:** • Recommendation: Justify the decision to model a 50 g post-weanling rat instead of examining internal dose for the period of newborn rat to mature mating rat. • One Committee member questioned why the model was run for post-weanling rats at body weight of 50g rather than for the period of new-born rat to mature mating rat. Given that this simulation is to get an internal dose metric for a 2-generation study, running only this body weight is potentially losing any changes in predicted internal dose due to the growth of the rat. Also, running the model from newborn rat to mating adult continuously better accounts for what the actual internal dose metric would be at mating. • In Section 3.2.5.2 (NMP risk evaluation, p. 197, lines 4615-4617), it states that the internal dose metrics for young post-weanling rats are the lowest. It would be useful to see a table to demonstrate this. **PUBLIC COMMENTS:** • EPA should use a duration-weighted average dose to NMP over the total exposure period (pre-mating, mating, gestation, lactation) as the basis for BMD modeling and also revisit the assumption of early-life susceptibility for the assessment of fertility effects, or adopt a different endpoint that is more directly	EPA is not able to model internal blood concentrations of NMP in newborn rats because the PBPK model does not include lactation and cannot predict NMP concentrations in milk. This means that it is not possible to calculate average exposures over the entire exposure period. Instead, EPA modeled internal exposures for post-weaning rats consuming known levels of NMP through food. Of the exposures that could be predicted in the PBPK model, the exposures predicted during the post-weaning life stage are the lowest that occurred throughout the exposure period. Because metabolism is assumed to scale allometrically (a standard assumption that is hard coded into the PBPK model), the metabolism/kg BW is higher for smaller animals, leading to a lower internal dose. Internal doses simulated for the Exxon 1991 study are included in Section 5.2 of *Risk Evaluation for N-Methylpyrrolidone (NMP), Benchmark Dose Modeling Supplemental File. Docket EPA-HQ-OPPT-2019-0236* (U.S. EPA, 2019a). A reference to this documentation is now included in the risk evaluation. It is not possible to determine which phase(s) of exposure were most sensitive to NMP and most contributed to the reduced fertility in the study. It is also unknown how sensitive phases in rat reproductive development translate to specific phases of sensitivity in humans. EPA assumed that any phase of the exposure could have been responsible for the effect and therefore selected the lowest dose predicted in the PBPK

	applicable to adult worker and consumer exposures. • EPA did not adequately consider rat size and associated internal dose within the context of its assumption of early-life susceptibility, which results in a nearly 2-fold increase in the estimated NMP potency. Because male rats in the Exxon (1991) study grew to >700 g (*i.e.*, well above the maximum weight of 450 g included in the table), Table 4-1 should be expanded to include doses for larger rats. • Inspection of the BMD modeling results in Table 4-4 of EPA's Benchmark Dose Modeling Supplemental File demonstrate a consistent pattern between points of departure for P2/F2A vs. P2/F2B litters for endpoints in both male and female animals (Table 5). This pattern is consistent with a duration effect, not an early life-stage effect.	model over the course of the exposure period as the basis for BMD modeling.
SACC	**SACC COMMENTS:** • Recommendation: Clarify how the PBPK model accounts for exposure during lactation. • It is not clear how the PBPK model accounts for exposure during lactation when there is no lactational component in the PBPK model. Exposure during this time period and its effect on internal doses are lost.	The PBPK model does not account for offspring exposure through lactation. The model estimates maternal blood concentrations but cannot predict milk concentrations or fetal exposures. As stated above, this is one reason why doses are based on 50 g post-weaning rats rather than rats exposed through lactation.
SACC	**SACC COMMENTS:** • A figure showing rat dermal PBPK predicted versus observed pharmacokinetic data should be included for completeness.	This is shown in Figure 4 in Appendix J.
PBPK modeling – Application of the PBPK model to estimate human occupational exposures		
SACC	**SACC COMMENTS:** • Recommendation: Justify the assumption of no	EPA assumes that dermal NMP exposure is constant. Rather than assuming that a specific amount of NMP is applied just

	decrease in coverage of NMP chemical on the surface of the skin over time due to absorption or evaporation.	once in a shift and that a set fraction of that will be absorbed, EPA assumes that over the course of a work shift, additional exposures may continue to occur (replacing what might be lost to absorption or evaporation). Evaporation from skin would only be applicable in scenarios where gloves are not used. For all COUs where gloves are worn, the dermal load of NMP that comes in contact with skin under gloves is only reduced by absorption (as evaporation is prevented by gloves). Glove protection factors already adjust for the reduction in exposure that may be provided by glove use in these scenarios. For all of the COUs, there is insufficient data on the frequency of new exposures that occur over the course of a shift. EPA's assumption of continuous exposure could contribute to an overestimate of risk for some COUs if dermal exposure occurs less frequently, but would not underestimate risk.
SACC	**SACC COMMENTS:** • Clarify whether the data referenced in the Semiconductor Industry comments at the Committee meeting are useful in reducing uncertainties in PBPK model inputs on exposure. • Clarify why the permeability coefficient (Kp) for dermal absorption was refit to the *in vivo* data, $4.7x10^{-3}$ versus $4.6x10^{-3}$. • Clarify why the sex difference in rats observed in plasma NMP levels over time, as seen in the data by Ghantous (1995), is not reflected in the PBPK model simulated trend presented in Figure_Apx_I4.	Regarding PBPK occupational inputs, EPA has included data and assumptions provided in semiconductor industry comments in many PBPK runs for occupational exposures. While weight fraction data provided in semiconductor industry comments reduce uncertainties, EPA cannot determine whether uncertainties in PBPK model inputs on exposure are reduced by using assumptions provided in semiconductor industry comments because EPA has no data to determine whether the proposed industry assumptions are more accurate than the assumptions applied by EPA. As described in the "*Dermal Model & Data*" section of Appendix J, an error was found in the Poet et al. (2010) model equations for dermal absorption (they did not account for bidirectional diffusion). Therefore, the parameter was re-fit to the dermal data after the equation was corrected. To the extent that sex differences in physiological parameters are known for rats, the rat parameters were set to those for female rats, given the focus on developmental exposures.

		Brown et al. (1997), a standard source for physiological parameters, does not report sex-specific differences for any tissues in rats other than those for gonads. Thus, the only physiological difference between males and females in model inputs is BW, which has a relatively small effect on predicted dose, as shown. While it would be possible to fit sex-specific metabolic rates to those data, given the focus on developmental effects, the model fits focused on female rats were considered adequate for dose-response assessment.
31	**PUBLIC COMMENTS:** • Tables 2-66 and 2-67, pp. 131-132: EPA should explain how acute exposure peak blood concentrations (in mg/L) and chronic exposure AUC values (in hour-mg/L) were determined for fab workers and maintenance.	EPA has clarified in the introduction to Section 2.4.1.3 that Table 2-77 (had been Table 2-67 in the draft risk evaluation) PBPK exposure results include acute exposures, which are peak blood concentrations (Cmax in mg/L), and chronic exposures, which are area under the curve (AUC in hr mg/L). EPA has provided updates to Tables 2-76 and 2-77 in the risk evaluation that include updated PBPK input parameter sets and results, including for fab workers and maintenance in the semiconductor industry. Input selection for the PBPK model that estimates the acute and chronic exposures values are shown in Section 2.4.1.2 for all OESs, and the semiconductor industry is covered in 2.4.1.2.10.
52	**PUBLIC COMMENTS:** • While many aspects of the 2019 EPA NMP PBPK model are adequately supported by primary and secondary peer reviewed literature, the use of the model to assess dermal liquid exposures lacked reference to sufficient peer reviewed or scientific consensus information.	While there are differences in the details, the model is in most aspects that which has been described in the peer review literature by Poet et al. (2010), which includes predictions for dermal exposures. Recognizing that while peer reviewed scientific publications are an indicator of quality, but are not entirely sufficient to determine a model's suitability for regulatory application, the U.S. EPA looks to and expects that its external review process, this SACC review in particular, will provide a sufficient level of peer review for the entirety of a risk analysis, including but not limited to any PBPK modeling used. However, per EPA policy, consensus among the peer review panel is not required.

52	**PUBLIC COMMENTS:** • EPA stated an intention in the draft risk evaluation to use a higher dermal permeability constant for neat NMP exposures, but appears to have used the lower dilute NMP permeability coefficient irrespective of weight fraction (EPA, 2019a). • Use of the higher permeability constant did not impact the conclusion of this assessment. It is noted that the increased permeability associated with neat NMP skin contact is unlikely to occur in the semiconductor industry because potential exposure events are transient, and likely do not occur every shift.	EPA appreciates the thoroughness of the review and the fact that this mistake was identified. In the expectation that absorption (permeability, PVL) will be a continuous function of the concentration of NMP in an aqueous solution – it would not change suddenly to a large extent when a solution changes by 1% weight fraction (WF) – EPA believes that setting permeability to be a continuous function of WF fraction is the most realistic approach. Since data are only available for two weight fractions, 50% and 100%, EPA believes the best resolution is to assume PVL is constant at the value estimated from the 50% WF data for concentrations below 50% and that the PVL increases linearly with concentration between 50% and 100%, as indicated by the lines in the graph. Model simulations and margin of exposure calculations were revised based on this assumed relationship. The 2nd comment is not entirely correct. There is no evidence that the duration or frequency of contact would have an impact on permeability. Hence a higher value of PVL will be used for exposure to concentrations over 50%, as described above, whether the exposure is transient and does not occur daily or is expected to occur for longer periods on a daily basis.
52	**PUBLIC COMMENTS:** • The density of NMP is not defined as static variable in the .m file of the 2019 EPA code. Thus, if the model is executed in a new acslX workspace, it is necessary to explicitly define density in the script file.	Since the density of NMP is set in the initial block of the .csl file, and is a physical constant that doesn't change, it does not need to be defined in a script. If a new acslX workspace was created with this CONSTANT statement in the initial block of the csl, the value will be correctly set. However, since acslX software has been discontinued, EPA does not expect such an event to occur. Future versions of the model would need to be created in a different software.
52	**PUBLIC COMMENTS:** • A correction to the skin:blood partition coefficient had not been documented in the supplemental materials of the Poet et al. (2016) human model code.	As described above, the EPA PBPK model differs from the PBPK model published by Poet et al (2016). See Appendix J of the risk evaluation for skin:blood partition coefficient used in the current model and a description of changes made to the

		dermal model.
BMD modeling – Model fit		
SACC, 57	**SACC COMMENTS:** • Recommendation: Reexamine the dose-response fit to the combined Saillenfait et al. (2003, 2002) data on resorptions in rat. Fit a dose-response to each dataset separately and compare the final POD estimate to that obtained for maternal toxicity for corroboration. • The placement (hence the calculation) of the benchmark dose (BMD) and benchmark dose level (BMDL) is not intuitive and appears far to the right of an apparent threshold (see p. 23, EPA, 2019f). The final model fit could be due to an artifact of combining results from two studies. The highest modeled dose appears to be driving this model. For some Committee members, these findings raised questions of the utility of the BMDL for this endpoint. Some Committee members questioned whether this effect is real (due to a threshold for maternal toxicity), an artifact from issues associated with study design and/or quality, or due to random variability (Type II error; false positive). The Committee suggests that EPA consider modeling the data for each study separately, after reevaluating the studies for confidence in the results (Saillenfait et al., 2002, 2003). **PUBLIC COMMENTS:** • In Table 3-3-2 in Section 3.1 of the draft assessment report (EPA, 2019a), EPA acknowledges that none of the models had an acceptable p-value of >0.1.	EPA has revised BMD modeling for post-implantation loss (resorptions and fetal mortality) and reduced fetal body weight to ensure appropriate model fits. The revised BMD modeling resulted in a new acute POD of 437 mg/L C_{max}. Revised models are summarized in Section 3.2.5.6 of the risk evaluation and described in detail in the revised BMD supplemental file. EPA revised the dose-response and risk characterization portions of the risk evaluation to reflect changes in the BMD analysis, the resulting PODs, and revised risk estimates. Specifically, for the acute POD, EPA considered the post-implantation loss data from the Saillenfait et al. (2002) and (2003) studies both independently and as a combined dataset. EPA analyzed results from the Saillenfait et al. (2003) inhalation study and, consistent with the study authors, found no statistically significant effect at any of the doses tested. Because there was not a statistically significant dose-response observed in the Saillenfait et al. (2003) post-implantation loss dataset, EPA did not consider using BMDs or BMDLs derived from this dataset alone as an acute POD. The internal doses achieved in the Saillenfait et al. (2003) inhalation study were all below the internal doses achieved in the Saillenfait et al. (2002) oral study. In order to provide a more robust dataset that includes dose-response information at the lower end of the dose response curve, EPA performed BMD modeling on the combined dose-response data from the oral and inhalation studies. EPA also performed BMD modeling on the Saillenfait et al. (2002) oral study alone. The combined model incorporates a more complete set of dose-response data, maximizing the power of the model and reducing the risk of

		overinterpreting statistical noise at the lower end of the dose-response curve. Prior to conducting BMD modeling on the post-implantation data, EPA applied a Rao-Scott transformation to adjust for litter effects in the absence of access to individual animal data. Using this approach, good BMD model fits were achieved for both the combined dataset and for the 2002 oral exposure data alone. Ultimately the BMDL identified in the combined dataset was identical to the BMDL identified in the Saillenfait et al. (2002) study alone (*i.e.*, a BMDL of 437 mg/L C_{max} was identified for both datasets). This is the POD EPA ultimately selected as the basis for risk characterization for acute exposures. The maternal effects reported in these studies do not negate the observed embryonic and fetal toxicity. Without additional information, it is difficult to determine if the maternal toxicity contributes to or is independent of the developmental effects. In addition, maternal toxicity in this study would be considered indicative of repeated dose effects relevant for derivation of the chronic POD rather than the acute POD. In the Saillenfait 2002 study, significant effects on fetal body weight (which are considered relevant for the chronic POD) occur below doses at which significant effects on maternal body weight were reported.
BMD modeling – BMR selection		
SACC, 33, 57, 63, 54	**SACC COMMENTS:** • Recommendation: Consider revising the BMR for fetal resorptions to a value >1% to avoid a BMDL that extrapolates far outside the range of observed responses. • The BMR of 1% results in a BMDL that is well below the level where a statistical effect was observed. Other BMRs tested (0.5 and 1 standard deviation [SD]) may be more appropriate. EPA guidance indicates that a	EPA selected a benchmark response (BMR) of 1% for post-implantation loss (resorptions and fetal mortality) to reflect the severity of the endpoint. This approach is consistent with the general principles for BMR selection that are outlined in EPA's BMD modeling guidance. For quantal data, the guidance describes a BMR of 10% extra risk as standard, but notes that "biological considerations may warrant the use of a BMR of 5% or lower for some types of effects (*e.g.*, frank effects)." Selection of a BMR of 1% for post-implantation

	$BMDL_{10}$ is always provided for comparison but was not observed for resorptions. **PUBLIC COMMENTS:** • The decision to adopt a BMR of 1% relative deviation (RD) in determining the POD (BMDL1RD) value for fetal resorptions is not supported by the data for NMP and is inconsistent with standard practice and EPA guidelines. • Summit Toxicology conducted supplemental BMD analyses for the acute toxicity of NMP. Based on these analyses, it is recommended that EPA adopt a BMR of 0.5 SD in dose-response analysis for the acute toxicity of NMP (acceptable model fit was achieved). • Even if one ignores the fact that the goodness of fit for all EPA model runs of the combined data is unacceptable per EPA BMD guidelines (*i.e.*, <0.0001 when it should be >0.1), a conservative BMR of 0.5 SD more than doubles the BMDL (*i.e.*, from 216 to 514).	loss is also consistent with IRIS assessments for TCE and 1,2,3-trichloropropane which applied 1% BMRs for prenatal loss, cardiac malformations, and reduced numbers of live pups/litter. EPA selected the BMR based on the severity of the endpoint (pregnancy loss) and not based on the statistical power of key studies. As EPAs BMR guidance states, "It is important to recognize that the BMR need not correspond to a response that the study could detect as statistically significantly different from the control response provided that the response is considered biologically significant." (page 20 of EPA's Benchmark Dose Technical Guidance). The available NMP studies do not have sufficient power to detect a 1% difference in post-implantation loss. EPA concluded that the lack of power in the key studies introduces uncertainty into the analysis but does not require application of a less cautious BMR.
BMD modeling – Software versions		
SACC, 57	**SACC COMMENTS:** • At least two different versions of EPA's Benchmark Dose Software (BMDS) appear to have been used (versions 2.7 and 3.1.1) • The Committee found it disconcerting that some nested dichotomous models examined are not included in BMDS 3.1.1, and EPA has provided no justification for this exclusion. • The Committee wondered if analysis results would be the same performed using BMDS 2.7 as obtained using BMDS 3.1.1 and the EPA-preferred NLogistic nested dichotomous model.	As detailed in the updated BMD Modeling Supplemental File, EPA used BMD software (BMDS) package versions 3.1.1 (released 07/31/2019), 3.1.2 (released 11/08/2019), or 3.2 (released 08/20/2020) to model post-implantation loss, resorptions, fetal and pup body weight changes, male fertility and femal fecundity, and absolute testes weight datasets. For these endpoints, choice of BMDS was dictated by software availability at the time of BMD modeling. As each BMDS release provides updates, fixes, and enhancements to BMDS version 3, EPA chose to use the most up-to-date BMDS version available when BMD modeling was originally conducted. Because there weren't major updates (*i.e.*, updates

	• The Committee questions why different versions of BMDS were used for the acute BMDs than for the chronic BMDs. The text states why two different versions were used for the chronic BMDs but not why a third version was used for the acute BMDs. **PUBLIC COMMENTS:** • It is recommended that EPA rely upon the latest version of BMDS in their TSCA risk assessment for NMP. • In addition, since variance does not appear to vary in a systematic manner as a function of dose, an assumption of constant variance should be considered.	that would significantly alter BMD results) made to the various releases of BMDS version 3 used in the NMP risk evaluation, EPA chose not to rerun all BMD modeling with the most up-to-date software (*i.e.*, BMDS 3.2). A complete history of updates made to various BMDS 3 releases is available here. The pup death and stillbirth endpoints were modeled using BMDS version 2.7 (released 08/18/2017) because it contains a larger suite of nested dichotomous models compared to BMDS version 3, and nested dichotomous models are preferred for these endpoints because they contain an intra-litter correlation coefficient for the assessment of litter-specific responses. Both BMDS 2.7 and BMDS version 3 contain the same NLogististic model, which is preferred because it has received more extensive QA testing and is deemed to be the most reliable nested model. In contrast, the NCTR and RaiVR nested dichotomous models are included in BMDS 2.7, but not BMDS version 3. Because BMDS 2.7 and BMDS version 3 contain the same version of the preferred NLogistic model, and because BMDS 2.7 contains the additional nested dichotomous models, BMDS 2.7 is preferred over BMDS version 3 to model pup death and stillbirth endpoints. For BMD modeling, EPA first assumed responses to be normally distributed with constant variance across dose groups. If no model achieved adequate fit to response means and response variances under those assumptions, models that assume normal distribution with modelled (*i.e.*, non-constant) variance were applied.
Dose-response analysis - Integration of data across exposure routes		
SACC	**SACC COMMENTS:**	EPA did not evaluate risks from NMP inhalation exposure independently. For NMP, EPA used the PBPK models to evaluate risks based on internal blood concentrations resulting

	• Recommendation: Justify why oral data are used to estimate inhalation risk when adequate inhalation data are available. • The Committee questioned the use of oral data to estimate inhalation risk when good inhalation data are available. Added to this is the statement that reports that excreted amounts of NMP metabolites are higher after inhalation dosing than after oral dosing (NMP risk evaluation, Section 3.2.5.5, p. 199, lines 4727-4729). These differences in excretion also support the Committee's conclusion that combining the Saillenfait oral and inhalation study data might not be appropriate. The same reason given in Section 3.2.5.6 (NMP risk evaluation, p. 205, lines 4916-4921) for why these studies were not combined for decreased fetal body weight might also apply as a reason for not combining these study data for the "acute" endpoints.	from combined exposures across all exposure routes. Rather than identifying separate PODs for each route of exposure, EPA derived a single set of acute and chronic PODs in terms of internal blood concentrations. These PODs are designed to evaluate risks from the internal NMP concentrations resulting from simultaneous inhalation, dermal, and vapor through skin exposure routes for each condition of use. Differences in absorption associated with each route are accounted for in the PBPK model. The PBPK model also takes into account various elimination routes, including exhalation, metabolism, urinary elimination, and desorption from open skin, irrespective of the route of exposure. For the acute endpoint, inclusion of data from both inhalation and oral studies allowed EPA to make use of a more complete dose-response dataset that covers a wider range of internal doses. The inhalation study alone is either too low in dose-range or too limited in statistical power to identify significant effects on the acute endpoint, post-implantation loss. EPA included the 2003 data in the combined dataset to ensure that BMD modeling included data from lower dose range, but the 2003 data on its own could not serve as the basis for a POD.
Dose-response analysis - Assumptions and uncertainties		
54	**PUBLIC COMMENTS:** • Overall, EPA should provide a more robust discussion of the assumptions and uncertainties inherent in the dose-response assessment in the revised risk evaluation. In addition, EPA should consider whether alternative PODs and/or BMRs are warranted. A statement regarding the uncertainty in the appropriate dose metric and outcome response rate for resorptions should be added to the table.	In the final risk evaluation, EPA considers a range of PODs in Section 3.2.5.6 and provides a rationale for selection of each POD over the other PODs considered. In Section 3.2.6, EPA discusses uncertainties around dose metrics and endpoint selection as part of the overall confidence in the final PODs. A more detailed discussion of the rationale for specific BMD approaches, BMRs and model selection for each endpoint is included in the BMD supplemental file.

Dose-response analysis - Other suggestions		

SACC	**SACC COMMENTS:**
	• SACC suggests the following:
	  ○ Add the numbers for increased fetal mortality to Figures 3-2 or 3-3.
	  ○ The phrase "small difference" (NMP risk evaluation, Section 3.2.5.1, p. 195, line 4550) should be clarified; "small" is a relative term.
	• In Section 3.2.5.5 (NMP risk evaluation, p. 199, lines 4707-4710), it states that the PBPK model was run for humans to estimate internal doses, which were then compared to the rat internal doses. This sounds backwards from what is normally done. It should be explained.
	• The word "similar" (NMP risk evaluation, Section 3.2.5.6, p. 201, line 4828) could use more information (*e.g.,* show the values that are similar in parentheses after the statement).
	• More details should be given in the main text (NMP risk evaluation, Tables 3-10 and 3-11) as to how the PBPK model runs were conducted for the rat BMD modeling (*i.e.*, run as pregnant rat, non-pregnant, etc.).
	• In Table 3-10 (NMP risk evaluation, Section 3.2.5.6, p. 202), the lines for the Becci study and the Sitarek study (line for NOAEL) do not state whether the internal dose is Cmax or AUC.
	• Section 3.2.5.6 (NMP risk evaluation, p. 203, lines 4861-4865) states that a UF was included to account for human variability. A Monte Carlo analysis could be used (like with the MC assessment) to account for human toxicokinetic variability.
	• Section 3.2.5.6 (NMP risk evaluation, p. 205, lines 4903-4914) discusses how data may possibly be
		Thank you for the suggestions.
		• The exposure-response arrays (now figures 3-2, 3-3, 3-4 and 3-5) have been expanded to include additional reproductive and developmental endpoints for easier comparison across endpoints.
		• As described above, EPA added a sentence with additional quantitative information from the van Raaij study to support the phrase "small difference."
		• The first paragraph in Section 3.2.5.5 was revised for clarity.
		• In Section 3.2.5.6, the word 'similar' is now followed by the specific values being compared in parentheses.
		• More details have been added to the narrative and to table footnotes to clarify the specific dose metrics used as the basis for BMD modeling for each endpoint.
		• Table 3-10 has been modified to specify that NOAELs from the Becci and Sitarek studies are in terms of Cmax.
		• EPA did not perform Monte Carlo analysis because there is insufficient quantitative information on the range of human variability to support such an analysis.
		• Whole body inhalation studies were considered as part of the weight of the scientific evidence and some endpoints were further evaluated in dose-response analysis. While there is uncertainty around specific levels of exposure achieved in these studies, the studies demonstrate that developmental effects are consistently observed across exposure routes. Data from these inhalation studies provide supporting evidence, but they did not provide the quantitative basis for PODs. The modeling for the acute POD incorporated data from the Saillenfait 2003 study but

	compromised due to condensation of NMP in whole body inhalation experiments and subsequent oral consumption by the exposed rats. Should this then eliminate whole body inhalation studies from consideration or is there sufficient information to show that it was not an issue for any inhalation studies used in the risk evaluation? The rationale for inclusion should be presented.	is really driven by the oral exposure data (demonstrated by the fact that the BMDL for the combined analysis is the same as the BMDL for the Saillenfait 2002 study alone). The chronic POD is based on effects on fertility in a two-generation dietary study.

7. Risk Characterization

Risk Characterization		
Charge Question 6.1: Please comment on whether the information presented to the panel supports the conclusions outlined in the draft risk characterization section concerning NMP. If not, please suggest alternative approaches or information that could be used to further develop a risk estimates within the context of the requirements stated in EPA's Final Rule, Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act (82 FR 33726). **Charge Question 6.2:** Please comment on the validity of specific confidence summaries presented in Sections 4.2 and 4.3. **Charge Question 6.3:** Please comment on any other aspect of the human health risk characterization that has not been mentioned above. **Charge Question 6.4:** Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the acute and chronic risks associated with occupational and consumer use of NMP-containing products, including the MOEs calculated with PBPK-derived internal doses. Please comment on the selection of composite uncertainty factors that were used to derive benchmark MOEs risk estimation. **Charge Question 6.5:** Please comment on this approach to evaluating the relative contribution of each exposure route to aggregate risk. **Charge Question 6.6:** Please comment on whether the risk evaluation has adequately addressed potentially exposed or susceptible subpopulations. **Charge Question 6.7:** Please comment on whether the risk evaluation document has adequately described the uncertainties and data limitations associated with the methodologies used to assess the human health risks. Please comment on whether this information is presented in a clear and transparent manner. **Charge Question 6.8:** Please comment on whether EPA has adequately, clearly, and appropriately presented the reasoning, approach, assumptions, and uncertainties for characterizing risk to workers using PPE.		
#	**Summary of Comments for Specific Issues Related to Charge Question 6**	**EPA Response**
Ecological Risk		
SACC	**SACC COMMENTS:** • Recommendation: Provide more detail on the selection of environmental receptors and better justify not considering risks to terrestrial organisms via surface waters. • The Committee agreed that the risk characterization section does not support clearly the conclusion of no unreasonable risk for aquatic organisms, and recommends further justification of the estimates used, adding UFs where	During problem formulation, EPA performed a first-tier screening analysis of risks from ambient air, ambient water, sediment, and land-applied biosolids. EPA did not identify risks from environmental exposures that may result from these pathways. In the final risk evaluation, EPA updated the evaluation of risks to aquatic life from ambient water exposures using more recent TRI release data. As described in Section 4.1, EPA did not identify risks to environmental receptors or the general population from ambient water.

	needed, and discussing further those scenarios where risk quotients are close to 1.	
Occupational Risk - ONUs		
SACC	**SACC COMMENTS:** • Lack of exposure data for ONUs is a major issue. • Recommendation: Explore and expand the use of modeling approaches to exposure estimation when exposure measurement data are insufficient or lacking (*e.g.*, workers and ONUs for NMP).	EPA has added to 2.4.1.1 that EPA has modeled inhalation air concentrations for workers in 11 of 17 OESs and far-field inhalation air concentrations for ONUs in 1 of 17 OESs. EPA has exhausted all modeling opportunities with the data that are reasonably available and therefore was unable to model inhalation air concentrations for workers in 6 OESs and far-field inhalation air concentrations for ONUs in the 16 OESs. However, air monitoring data for workers was available and used for workers and ONUs when modeling was not possible.
Occupational risk – Self-employed and small businesses		
55	**PUBLIC COMMENTS:** • A risk determination for workers and ONUs, both self-employed and in small businesses, that incorporates OSHA's exemptions and practical exceptions should be added to the risk evaluation.	EPA does not have reasonably available data or information to distinguish how OSHA's exemptions and practical exceptions would cause exposure differences for workers and ONUs, both self-employed and in small businesses.
Benchmark MOEs – Uncertainty factors		
SACC, 33, 57	**SACC COMMENTS:** • Recommendation: Consider deriving data-driven extrapolation factors (DDEFs) as an alternative to default UFs. **PUBLIC COMMENTS:** • Based on PBPK modeling of individual data from human volunteers exposed via inhalation (reflects uptake via inhalation and dermal absorption of vapor) to three concentrations of NMP vapor (Bader and van Thriel, 2006), peak NMP levels in blood (mg/L) for each exposure concentration were determined to have a coefficient of variation (CV) of approximately 0.21, while AUC blood	EPA expects that DDEFs would result in very similar total UFs as the default UFs that are already applied for NMP. In addition, the analysis presented in public comments is based on a small sample of healthy workers (n=7) described in Bader and van Thriel (2006). EPA concluded that this small dataset is not sufficient as the basis for defining the potential range of toxicokinetic variability across the population. In the absence of data that adequately captures the true variability in the population, EPA applied default uncertainty factors for interindividual variability. Therefore, rather than identifying benchmark MOEs of 20 and 21 as suggested by commenters, EPA identified a benchmark MOE of 30 for acute and chronic exposures.

	levels (mg/L × h) for each exposure concentration had a CV of approximately 0.28 (Poet et al., 2016). • Using the CV for peak blood levels and assuming a normal distribution in a healthy worker population, a tk DDEF of 2.0 (1.21 × 1.645, rounded to two significant figures) is judged sufficient to protect 95% of a healthy worker population and yields a net UFH of 6.3 [2.0 (tk) × 3.16 (td)]. Using the CV for AUC data similarly, a DDEF of 2.1 (1.28 × 1.645) and a net UFH of 6.6 [2.0 (tk) × 3.16 (td)] can be calculated. When these net UFH values are combined with the UFA value of 3.16, the composite UFs for acute (peak) and chronic (AUC) exposures to workers are 20 (6.3 × 3.16) and 21 (6.6 × 3.16), respectively. • For occupational scenarios, the default MOE of 30 should be replaced by data-driven MOEs of 20 (acute exposures) and 21 (chronic exposures)	
SACC, 34, 38, 51, 59, 61	**SACC COMMENTS:** • Recommendation: Consider utilizing UFs for database completeness and quality in TSCA chemical evaluations. **PUBLIC COMMENTS:** • EPA's benchmark MOEs for acute and chronic effects should include a further UF of 10 for database uncertainty (data gaps include immune system, neurotoxicity, reproductive, endocrine, and/or developmental endpoints). • EPA should be using its information gathering authorities to fill the data gaps or, at a minimum, should apply an additional 10X UF to account for these database deficiencies. • Fetal death is a severe endpoint, not a sensitive one, and EPA must acknowledge with appropriate UFs that many adverse effects will occur at lower doses.	There is no universal list of hazard data required when evaluating chemical risks under TSCA. Furthermore, for NMP, EPA has sufficient, reasonably available hazard information to conduct a risk evaluation and support the use of the chosen hazard endpoints. Therefore, EPA did not use a database uncertainty factor in the NMP risk evaluation. EPA acknowledges the severity of the post-implantation loss endpoint and applied a BMR of 1% in benchmark dose modeling.

34, 51, 38	**PUBLIC COMMENTS:** • EPA should provide justification for its deviations from its standard inter- and intra-species UFs, or utilize the default value. • It is recommended that EPA apply a UF of at least 20X for intraspecies variability to account for the known susceptibility of some subpopulations to NMP's developmental and reproductive effects. • To provide protection for developmental effects that occur at doses below those causing death, a UF beyond the default intraspecies 10X factor should be applied, as EPA has previously done for other susceptible groups such as infants and children.	EPA typically considers the interspecies uncertainty factor of 10 to be comprised of a factor of 3 to account for toxicokinetic differences and a factor of 3 to account for toxicodynamic differences. As described in Section 3.2.5.6 of the final risk evaluation, toxicokinetic differences between rats and humans are already accounted for in PBPK modeling. EPA therefore applied a total interspecies uncertainty factor of 3 to account for toxicodynamic differences for both acute and chronic PODs. Consistent with standard practice, EPA also applied the default intraspecies uncertainty factor of 10 to both acute and chronic PODs to account for sensitive subpopulations.
38, 51	**PUBLIC COMMENTS:** • EPA should apply a UF of 10 to reflect the absence of a NOAEL for NMP's reproductive effects. The full UF of 10 for LOAEL-to-NOAEL extrapolation should be applied since there is no basis for reducing it.	EPA applies uncertainty factors for LOAEL to NOAEL extrapolation when a LOAEL serves as the point of departure. To derive the chronic POD for NMP, EPA used BMD modeling to identify a BMDL as the point of departure. EPA does not apply LOAEL to NOAEL uncertainty factors when PODs are derived from BMD modeling, because BMD modeling addresses many of the limitations associated with the NOAEL/LOAEL approach.
MOE determinations based on updated PBPK modeling (Cardno ChemRisk)		
52	**PUBLIC COMMENTS:** • Based on Cardno ChemRisk analysis, there is not an unreasonable risk in the unlikely event that neat NMP were to contact the palm side of two gloved hands (plausible acute worst case). • EPA conclusions regarding unreasonable risk for the use of NMP in semiconductor manufacturing reflected the lack of refinement and use of incorrect assumptions in the screening. • The Cardno ChemRisk analysis indicates a differentiation on exposure potential between jobs, with some functions having	EPA does not have reasonably available information and data to verify parameter assumptions in the Cardno ChemRisk analysis. EPA also did not identify reasonably available information or data indicating that any of the assumptions EPA used in the analysis are incorrect. For the Semiconductor manufacturing OES (Section 2.4.1.2.10), EPA revised and expanded PBPK runs for industry-specific work activities using industry-specific sets provided in public comments

	no opportunity for dermal direct contact. The resultant acute and chronic MOEs were >30, indicating support for a conclusion that use of NMP in the semiconductor industry does not present an unreasonable risk.	for the semiconductor manufacturing industry. As demonstrated by various PBPK parameter sets, the EPA analysis indicates a differentiation on exposure potential between jobs as does the Cardno ChemRisk analysis. EPA's analysis uses ONUs to indicate functions having no opportunity for dermal direct contact.
PPE assumptions – General		
SACC	**SACC COMMENTS:** • Recommendation: Provide a more balanced description of exposures and MOE estimates with and without PPE in the text of Section 4 to reflect the estimates provided in the tables. • Recommendation: Provide a balanced description of risk with and without PPE use in the text of Section 4. • The risk characterization section (Section 4) does not provide a clear summary of the rationale, approach, assumptions, and uncertainties about PPE, which are more clearly described in other sections of the draft risk evaluation. • The text referring to the values in the tables of Section 4 occasionally neglects to discuss MOEs when PPE use is not assumed, resulting in an unbalanced discussion of the information presented in the tables.	In Section 4, risks for occupational exposures are calculated and presented both with and without PPE to provide risk managers and the public with complete information about how PPE use could influence risk. In Section 4.2.2 of the risk evaluation, EPA presents risk estimates for occupational exposures both with and without glove use (glove PFs 1, 5, 10, and 20) for each occupational exposure scenario. Table 4-54 presents risk estimates with and without gloves and respirators for all conditions of use. The narrative in Section 4.6.2.1 describes risk with and without glove use.
61	**PUBLIC COMMENTS:** • EPA's assumption of PPE use violates TSCA's requirement to "use scientific … methods, protocols, [and] methodologies … in a manner consistent with the best available science." The best available science for occupational risk assessment requires the measurement of worker exposures and risks without PPE. • These non-PPE measurements permit OSHA and other regulatory agencies to determine whether risks can be	For the purpose of this risk evaluation, EPA makes assumptions about potential PPE use based on reasonably available information and expert judgment. EPA considers each condition of use and constructs exposure scenarios with and without engineering controls and /or PPE that may be applicable to particular worker tasks on a case-specific basis for a given chemical. While EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA will not assume that workers are unprotected by PPE

	eliminated through the use of engineering controls and hazard elimination before the consideration of PPE, consistent with the well-established occupational hierarchy of controls.	where such PPE might be necessary to meet federal regulations, unless the Agency has evidence that workers are unprotected. For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on information and judgement underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in Section 5.2. Additionally, in consideration of the uncertainties and variabilities in PPE usage, including the duration of PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determinations in order to address those uncertainties. EPA has also outlined its PPE assumptions in Section 5.1 and EPA's assumptions are described in the unreasonable risk determination for each condition of use, in Section 5.2. The OSHA regulations at 29 CFR 1910.132 require employers to assess a workplace to determine if hazards are present or likely to be present which necessitate the use of PPE. If the employer determines hazards are present or likely to be present, the employer must select the types of PPE that will protect against the identified hazards, require employees to use that PPE, communicate the selection decisions to each affected employee, and select PPE that properly fits each affected employee.
SACC	**SACC COMMENTS:** • Recommendation: Describe assumptions and uncertainties regarding PPE use, including how they differentially affect conclusions about risks for multiple occupational exposure scenarios. • There should be cross-referencing to Section 2.4.1.1 (Glove Use, NMP risk evaluation, pp. 68-69 and Table 2-3, p. 70),	In Section 2, EPA has removed assignments/ assumptions of specific glove PFs to apply to each OES. Table 2-77 has been updated to include worker exposures for all glove PFs for all OESs. To the extent that information is available on PPE use for specific occupational exposure scenarios, it is described in Section 2. In Risk Characterization (Section 4) EPA presents risks for all occupational exposure scenarios

	where PPE is discussed in detail. Tables 4-5 through 4-36 should indicate the category of glove use, for example, by adding footnotes linking to Table 2-3. (SACC provided a table of scenarios that are sensitive to glove use assumptions in their report) • The Evaluation should explicitly recognize that the assumed glove use and the GPF assignment have a major effect on MOEs for risk characterization in multiple occupational use scenarios, and describe the extent to which these assumptions and uncertainties about PPE use influence conclusions about risk.	both with and without glove use and with and without respirator use. In Section 4.2.2, in the discussion of strengths and limitations of risk estimates calculated for each OES, EPA describes glove use assumptions as a source of uncertainty. Table 4-54 demonstrates the extent to which gloves and respirators influence risk estimates for each condition of use.
31, 33, 56, 57	**PUBLIC COMMENTS:** • EPA assumptions of no PPE or ineffective PPE for the high-end exposure scenario should be justified. • The statement indicating that "high-end occupational exposure estimates for NMP use in cleaning, metal finishing, electronic parts manufacturing, automotive servicing, and use in (or removal of) paints, coatings, adhesives and sealants show risks that are not mitigated via glove use" is inaccurate. The SIA data submitted to EPA indicate that semiconductor risks ARE mitigated via glove use. • EPA's assumptions on worker exposure controls for "Use in Electrical Equipment, Appliance and Component Manufacturing" are not aligned with ongoing workplace practices and need to be re-evaluated.	In Section 2, EPA has removed assignments/ assumptions of specific glove PFs to apply to each OES. Table 2-77 has been updated to include worker exposures for all glove PFs for all OESs. EPA revised and expanded PBPK runs for industry-specific work activities using industry-specific data and information provided in public comments for the semiconductor manufacturing industry. To the extent that information is reasonably available on PPE use for specific occupational exposure scenarios, it is described in Section 2. In Section 4, EPA presents risks for all occupational exposure scenarios both with and without glove use and with and without respirator use. Table 4-54 demonstrates the extent to which gloves and respirators influence risk estimates for each condition of use.
PPE assumptions - Glove protection factors		
59, 57, 52, 49	**PUBLIC COMMENTS:** • EPA should utilize chemical-specific data for PFs of gloves that are likely to be used as PPE in industrial settings with NMP (Zellers and Sulewski, 1993; Stull et al., 2002; Crook and Simpson, 2007). Chemical-specific GPFs (Kirman,	EPA appreciates the commenters' recommendations and considered the information submitted concerning the use of chemical specific gloves and protection factors (PF) assigned to specific industries occupational exposure. In Section 2.4.1.1 of the draft risk evaluation EPA discussed the parameters and assumptions made about glove use and

	2020; Attachment 1) were provided with this comment (Docket 0057, comment 51). • The submitted report "Assessment of the Efficacy of Different Glove Materials for Reducing Potential Hazards Associated with NMP Containing Paint Strippers" was not listed among the references used by EPA in this assessment. Was this in error? • For lithium ion battery manufacturing and the semiconductor industry, EPA should assign a higher GPF (*e.g.*, PF 20) and recalculate the MOEs. • The strict work rules in the semiconductor industry and training programs support a GPF of 20 (95%).	associated protection factors (PFs) based on information including worker training and NMP chemical-resistant gloves. EPA recommends the commenters also refer to table 2-3 in the risk evaluation to review EPA's glove protection factors for different dermal protection strategies. For the purpose of this risk evaluation, EPA makes assumptions about potential PPE use based on reasonably available information and expert judgment. EPA considers each condition of use and constructs exposure scenarios with and without engineering controls and /or PPE that may be applicable to particular worker tasks on a case-specific basis for a given chemical. Again, while EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected. For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on information and judgement underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in Section 5.2. Additionally, in consideration of the uncertainties and variabilities in PPE usage, including the duration of PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determinations in order to address those uncertainties. EPA has also outlined its PPE assumptions in Section 5.1 and EPA's assumptions are described in the unreasonable risk determination for each condition of use, in Section 5.2. The chemical-specific glove PFs referred to in this comment were generated using a limited approach (in Kirman, 2020) using laboratory-generated data on

		permeation testing of NMP-containing liquids. Actual glove PFs holistically take into consideration other factors beyond permeation, including several listed in Section 2.4.1.1: NMP-based product that penetrates the gloves, including potential seepage through the cuff from improper donning of the gloves and the gloves may occlude the evaporation of NMP from the skin. EPA recognizes that the references "Zellers and Sulewski, 1993; Stull et al., 2002; Crook and Simpson, 2007" are covered by Kirman, 2020, and several of these references are cited in Appendix F of the risk evaluation. The report "Assessment of the Efficacy of Different Glove Materials for Reducing Potential Hazards Associated with NMP Containing Paint Strippers" noted in docket reference EPA-HQ-OPPT-2016-0231-0910, is apparently a pre-cursor to Kirman, 2020. This report uses a similar limited approach to Kirman, 2020, and data and PFs from these sources are not used in the risk evaluation and are therefore not listed among the references. In Chapter 2, EPA has removed assignments/ assumptions of specific glove PFs to apply to each OES. Table 2-77 has been updated to include worker exposures for all glove PFs for all OESs.
59, 52	**PUBLIC COMMENTS:** • For several conditions of use, EPA asserts that it used lower PFs than it actually relies on in its risk determinations, and there are contradictions within the text that are inconsistent with information that it relied on in its risk estimates table (Table 4-50) and risk determination table (Table 5-1). The PF used in the risk estimates should be clarified and stated consistently in text and tables.	EPA appreciates the commenters' suggestion and has worked to add clarity to the use of glove protection factors (PF) in the risk evaluation. Section 5.2 describes the PPE assumptions for each condition of use and how those assumptions contribute to the unreasonable risk determination. In other sections of the risk evaluation, EPA provides additional information on each occupational and consumer exposure scenario, shows risk estimates with a range of glove PF for workers, and describes the assumption of no PPE for consumers. EPA has outlined its

		PPE assumptions in Section 5.1 and has supplemented some sources and information in Section 2.4.1.1. of the risk evaluation and Appendix E Occupational Exposures. EPA has also added tables in Section 4.2.2 to clarify the PPE assumptions made for each COU. Additionally, in consideration of the uncertainties and variabilities in PPE usage, including the duration of PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determinations in order to address those uncertainties. In Section 4.2.2 of the risk evaluation, EPA presents risk estimates for occupational exposures both with and without glove use (glove PFs 1, 5, 10, and 20) for each occupational exposure scenario. Table 4-54 (formerly table 4-50) presents risk estimates with and without gloves and respirators for all conditions of use.
61	**PUBLIC COMMENTS:** • Without data on which gloves are provided to which employees, EPA has no basis for assuming specific GPFs in its draft risk evaluation.	EPA appreciates the comments. Whenever EPA had data on PPE and glove use for specific uses, we incorporated the information into the risk evaluation. EPA has outlined its PPE assumptions in Section 5.1 and has supplemented some sources and information on respirator use in Section 2.4.1.1. of the risk evaluation and Section 1.4.6 of the Supplemental Information on Releases and Occupational Exposure Assessment. EPA has also added a table in Section 4.2.2.1 to make the PPE assumptions made for each COU clearer. Additionally, in consideration of the uncertainties and variabilities in PPE usage, including the duration of PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determinations in order to address those uncertainties.
PPE assumptions – Glove use assumptions, OSHA guidance and SDS information		
42, 55, 51, 34,	**PUBLIC COMMENTS:** • EPA assumes that proper gloves will always be used for NMP handling, and that workers are trained in proper glove	In Chapter 2, EPA no longer uses professional judgment to predict the likelihood of the use of glove and has removed

59, 56, 61	use. No data or other evidence are presented to support this assumption.
	• In the NMP draft risk evaluation, EPA states that it "used professional judgment to predict the likelihood of the use of gloves … and the associated [protectiveness factors] are presented as what-if scenarios."
	  ○ It is not clear what this judgment is based on, given that EPA earlier states that it "does not know the likelihood that workers wear gloves of the proper type and have training on the proper usage of gloves," and that the "assumed glove protection factor values are highly uncertain."
	  ○ EPA provides no evidence that industry has conducted testing to identify the best glove materials for each of the many NMP-containing products and mixtures to which workers are exposed.
	• For several work scenarios (construction trades, small businesses, self-employed workers, etc.), widespread glove use is unlikely.
	• The unfounded assumptions that persons will always use gloves and that they will always effectively reduce risk have no evidentiary support in the administrative record. EPA cannot rely on OSHA regulations and use of gloves to reduce risk. TSCA requires the assessment of risk to workers in the absence of PPE, and if risks are identified, it can then be considered whether the risks would or would not be mitigated by PPE.
	• If glove use is non-existent or limited, risks to exposed workers would be unreasonable according to EPA's risk benchmarks and worker protections would be required under TSCA section 6(a). In its final risk evaluation, EPA should adhere to its own unreasonable risk criteria and not
		assignments/ assumptions of specific glove PFs to apply to each OES. Table 2-77 has been updated to include worker exposures for all glove PFs for all OESs.
		To the extent that information is reasonably available on PPE use for specific occupational exposure scenarios, it is described in Section 2.
		In Section 4, risks for occupational exposures are calculated and presented both with and without PPE to provide risk managers and the public with complete information about how PPE use could influence risk. In Section 4.2.2 of the risk evaluation, EPA presents risk estimates for occupational exposures both with and without glove use (glove PFs 1, 5, 10, and 20) for each occupational exposure scenario. Table 4-54 presents risk estimates with and without gloves and respirators for all conditions of use.
		For the purpose of this risk evaluation, EPA makes assumptions about potential PPE use based on reasonably available information and expert judgment. EPA considers each condition of use and constructs exposure scenarios with and without engineering controls and /or PPE that may be applicable to particular worker tasks on a case-specific basis for a given chemical. Again, while EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected. For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on information underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in Section 5.2. Additionally, in consideration of the uncertainties and

	recharacterize risks that meet these criteria as "reasonable" based on "uncertainty." • OSHA cannot cite an employer for failing to follow manufacturer recommendations in a Safety Data Sheet (SDS). In the absence of such a requirement, there is no basis for EPA's assumption that the Hazard Communication Standard will result in the uniform use of appropriate PPE.	variabilities in PPE usage, including the duration of PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determinations in order to address those uncertainties. EPA has also outlined its PPE assumptions in Section 5.1 and EPA's assumptions are described in the unreasonable risk determination for each condition of use, in Section 5.2.
33, 57	**PUBLIC COMMENTS:** • OSHA data support the position that workers use appropriate gloves and other PPE. It is therefore inappropriate for EPA to assess scenarios in which no gloves or the wrong glove types are used.	While EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected. In Section 2.4.1.1, EPA presented an example from a published report on a scenario, graffiti removal, in which no gloves or the wrong glove types are used.
51, 59, 61	**PUBLIC COMMENTS:** • For scenarios that involve only industrial sites, EPA inappropriately assumes that "SDS recommendations are followed and that workers are likely to wear protective gloves and have specialized training on the proper usage of these gloves, corresponding to a protection factor of 20" (p. 213). • EPA points out that SDSs for NMP and NMP-containing products recommend gloves (p. 68) and the NMP draft risk evaluation states that "EPA expects … [that] OSHA regulations for worker protection and hazard communication will result in use of appropriate PPE consistent with the applicable SDSs in a manner adequate to protect them" (p. 335). o No evidence is provided indicating that these SDSs are read by most employers, let alone shared with workers, or that their recommendations are consistently implemented.	Information reasonably available to EPA, including data submitted by chemical manufacturers and processors, indicates that PPE is generally used. EPA does not assume that the inclusion of PPE on SDSs is sufficient to ensure PPE use. While EPA considers the information on SDSs, EPA does not make PPE use assumptions based solely on SDSs. EPA generally assumes compliance with OSHA requirements for protection of workers, including the implementation of the hierarchy of controls. In support of this assumption, EPA used reasonably available information indicating that some employers, particularly in the industrial setting, are providing appropriate engineering, or administrative controls, or PPE to their employees consistent with OSHA requirements. EPA does not have reasonably available information to support this assumption for each condition of use; however, EPA does not believe that the Agency must presume, in the

	○ SDSs are often inaccurate, incomplete, and too technical for many workers to understand. • In its proposed 2017 rule to ban MC and NMP paint removers, EPA concluded that enhanced warnings and directions for use would not be effective because "consumers and professionals do not consistently pay attention to labels for hazardous substances; consumers, particularly those with lower literacy levels, often do not understand label information…." • A comprehensive survey of SDSs identified "a number of common themes … regarding inaccuracies, incompleteness, [and] incomprehensibility" and cautioned that "there are serious problems with the use of SDSs as hazard communication tools." • Even if gloves were worn by certain workers, EPA has little to no information about the types of gloves worn. Without data on which gloves are provided to which employees, EPA has no basis for assuming specific GPFs in its draft risk evaluation.	absence of such information, a lack of compliance with existing regulatory programs and practices. Rather, EPA assumes there is compliance with worker protection standards unless case-specific facts indicate otherwise, and therefore existing OSHA regulations for worker protection and hazard communication will result in use of appropriate PPE in a manner that achieves the stated APF or PF. EPA's decisions for unreasonable risk to workers are based on high-end exposure estimates, in order to account for the uncertainties related to whether or not workers are using PPE. EPA believes this is a reasonable and appropriate approach that accounts for reasonably available information and professional judgement related to worker protection practices, and addresses uncertainties regarding availability and use of PPE. In Sections 2 and 4, the risk evaluation presents exposure and risk estimates for each occupational exposure scenario both with and without glove use. To the extent that EPA has information about glove use in a specific industry, it is described in Section 2.4.1.2. In Section 4.2.2, EPA acknowledges that glove protection factors for each exposure scenario are a source of uncertainty for exposure and risk estimates.
PPE assumptions – Respirators		
42	**<u>PUBLIC COMMENTS:</u>** • The assumption that respirators are used by all exposed workers, under all conditions of chemical use and are 100% effective is erroneous. Respirators are considered to be less effective in protecting employees than other engineering and administrative controls (*i.e.*, NIOSH hierarchy of controls). • Employers are highly unlikely to institute a respiratory protection program without an express requirement (*i.e.*, no OSHA PEL).	EPA states in Section 2.4.1.1 that "Few literature sources indicate the use of respirators for reducing worker exposures to NMP by inhalation. Therefore, EPA central tendency and high-end scenarios do not incorporate protection factors for respirator use." PBPK results shown in Table 2-77 do not include reductions for respirator use. In Section 4, EPA presents risk estimates for each COU with and without gloves and respirators. As demonstrated by the risk estimates summarized in Table 4-54, respirator

	• The 8-hour use of PPE should not be used in the risk characterization.	use has minimal impact on overall risk estimates for workers exposed to NMP.
Potentially exposed or susceptible subpopulations		
SACC, 38, 51, 55, 54, 61	**SACC COMMENTS:** • Recommendation: Revise Section 4.4 to describe PESS consistent with how it is described in other sections of the draft risk evaluation and to be as specific as the descriptions used elsewhere in the document. • The statement "Due to limited information on the degree that humans of varying gender, age, health status, or genetic makeup might vary in the disposition of, or response to NMP a factor of 10 was applied" bears repeating in Section 4.4. • It would be helpful if the draft risk evaluation listed the categories of PESS described throughout the draft risk evaluation and use this list as a guide for the summary presented in Section 4.4 to assure completeness and consistency. • Section 4 should emphasize more the most critical population of concern (*i.e.*, pregnant women or women who could become pregnant). **PUBLIC COMMENTS:** • EPA must consider and analyze each of the following types of subpopulations: infants, children, pregnant women, workers, and the elderly. • Due to the developmental neurotoxicity risks, pregnant women, fetuses, and children should all be specifically included. • Due to the reproductive risks, reproductive aged men and women should be included. • Due to the risks for neurotoxicity, immunotoxicity, and other risks, elders and people with health conditions should be included.	In an effort to be concise and avoid repetition, Section 4.4 does not repeat everything stated in previous sections, but does provide references and links back to slightly more detailed discussions earlier in the document. All discussions of PESS are consistent, though previous sections go into slightly more detail. Section 4.4 lists the general categories of PESS considered in the risk evaluation. Consistent with the statement cited by the SACC, Section 4.4 has been slightly modified to state, "There is insufficient information to support a quantitative analysis of interindividual variability in other potentially susceptible populations. An uncertainty factor of 10 was applied to account for interindividual variability across gender, age, health status, genetic makeup, or other factors, but the actual effect of various factors contributing to biological susceptibility on overall risk is unknown." Although EPA agrees with the SACC that pregnant women and women who could become pregnant are a critical population to consider for developmental effects, they are not the only population that needs to be emphasized in this section. As described throughout Section 3, male exposure to NMP prior to conception may reduce reproductive success (by reducing male fertility and offspring survival). Children and adolescents may also be sensitive to reproductive effects, though the specific phases of development during which exposure may have the most impact is not known. Consistent with public comments, Section 4 highlights the potential susceptibility of pregnant women as well as both males and females of reproductive age, children and adolescents, and people with health

	• Individuals with chronic liver or kidney disease or other systemic ailments may be at particularly high risk for organ damage or other systemic adverse effects. Thus, workers or consumers at risk for developmental and reproductive effects may well also be at risk for liver and kidney damage, and vice-versa.	conditions or metabolic differences. Section 4.4 states, "The developmental effects identified as a critical human health endpoint for acute exposures in this draft risk evaluation are a major concern for pregnant women, the developing fetus, and women who may become pregnant. The reproductive effects identified as a critical human health endpoint for chronic exposures may be of concern for all people of reproductive age as well as for infants, children and adolescents whose reproductive systems are still developing. Other populations that may be more sensitive to the hazards of NMP exposure include people with pre-existing conditions, and people with lower metabolic capacity due to life stage, genetic variation, or impaired liver function. The magnitude of the effect of each of these factors alone or in combination on overall risk is unknown." While EPA does not have specific information on susceptibility of elderly people to NMP, they are more likely to have pre-existing conditions. Potential susceptibility to genetic variation and preexisting conditions related to neurotoxicity and immunotoxicity and other risks are specifically discussed in Section 3.2.5.4:"Genetic variations or pre-existing conditions that increase susceptibility of the reproductive system, the hepatic, renal, nervous, immune, and other systems targeted by NMP could also make some individuals more susceptible to adverse health outcomes following consumer or workplace exposures." Finally, EPA notes that TSCA Section 3(12) lists examples of human receptors that may be considered PESS but provides for EPA to identify the relevant subpopulations for each chemical substance. Infants, children, pregnant women, workers, and the elderly are examples of human

		receptors that may be identified as PESS in individual chemical risk evaluations.
SACC	**SACC COMMENTS:** • Recommendation: Consider formally calculating risk for the CYP2E1 susceptible subpopulation. • Biologically susceptible subpopulations, including variations in CYP2E1, other unidentified genetic variations, preexisting conditions in the liver and other organ systems, and other chemical co-exposures are discussed in adequate detail. This information should be more completely summarized in Section 4.4. • Many on the Committee concluded that there seems to be enough information to attempt calculating risks for the CYP2E1 susceptible subpopulation.	There is evidence that CYP2E1 contributes to NMP metabolism (Ligocka et al., 2003), suggesting genetic variation in CYP2E1 may increase susceptibility to NMP by altering metabolism. While there is quantitative information about variation in CYP2E1 expression across the population, there is insufficient information to predict the impact of that variation on risk. EPA does not have sufficient quantitative information about the magnitude of differences in NMP metabolism caused by genetic variation in CYP2E1. There is also insufficient quantitative information about variability of other metabolic pathways that may contribute to NMP metabolism. EPA concluded that there is not sufficient quantitative information about variation in NMP metabolism to incorporate this into the model. In the absence of more quantitative information, EPA assumes that an interindividual uncertainty factor of 10 (with a factor of 3 designated for toxicokinetic differences across individuals) is sufficient for addressing metabolic differences within the population. The potential role of CYP2E1 activity in increasing susceptibility is discussed in Section 3.2.5.3.
SACC	**SACC COMMENTS:** • Recommendation: Expand the discussion on PESS to include potential risks of developmental neurotoxicity in infants and impacts of lower CYP2E1 activity in fetuses/infants. • The discussion on PESS in the risk characterization section should include the following: ○ Infants: Postnatal endpoints are not directly addressed in the draft risk evaluation, but discussion of associated endpoints and risks could be incorporated if developmental neurotoxicity were considered.	EPA acknowledges the substantial uncertainty around the increased susceptibility to young infants due to differences in CYP2E1 expression in Section 3.2.5.3: "The variability in CYP2E1 in pregnant women could affect how much NMP reaches the fetus, which typically does not express CYP2E1 (Hines, 2007). Newborns and very young infants are particularly susceptible to NMP exposure because they are metabolically immature. CYP2E1 is not fully expressed in children until about 90-days of age (Johnsrud et al., 2003). The variability in CYP2E1 was identified as an

	○ Fetuses and infants: The draft risk evaluation does discuss concerns with enzyme CYP2E1 activity including a known mutation that can put fetuses and infants at risk, but risk characterization was not provided for this subpopulation. If this risk factor were considered, risk calculations would change with the result that the safety of this vulnerable population would become a concern.	important uncertainty that was reflected in the calculation of the intraspecies uncertainty factor (human variability)." As discussed in response to the previous comment, EPA does not have sufficient information to provide a quantitative analysis of the impact of this important metabolic difference on risk. To specifically address uncertainty related to developmental neurotoxicity and metabolic differences in the risk characterization section, EPA added the following statement to Section 4.4: "there is uncertainty around the impact of metabolic differences in young infants on susceptibility. There is also uncertainty around susceptibility of infants and young children to neurodevelopmental effects of NMP which have been documented in animals at high doses but have not been characterized at lower doses."
PESS – Tribal communities		
55	**PUBLIC COMMENTS:** • The multiple exposure scenarios associated with proximity to unlined disposal site releases to environmental media must be analyzed for both individual exposures and the cumulative exposures that tribal members face from their customary and traditional tribal lifeways (inhalation, dermal, ingestion). • As part of this analysis, EPA should identify all populations living near disposal and other waste management sites as potentially exposed subpopulations. Groups living near National Priority List (NPL) sites and proposed NPL sites should be included as well.	EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the scope of the risk evaluation for NMP using authorities in TSCA Sections 6(b) and 9(b)(1). As described in Section 1.4.2 of the risk evaluation, EPA did not include exposures via the drinking water pathway or disposal to underground injection, RCRA Subtitle C hazardous waste landfills, or RCRA Subtitle D municipal solid waste (MSW) landfills in this risk evaluation. These exposure pathways fall under the jurisdiction of other EPA-administered statutes and associated regulatory programs.

		Populations exposed through pathways excluded from the risk evaluation were not identified as PESS. EPA disagrees with public comments on the draft risk evaluation that suggest fenceline subpopulations should be identified as PESS. TSCA provides EPA with the discretion to identify the PESS that are relevant to the chemical-specific risk evaluation [TSCA Section 6(b)(4)(A)]. General population exposure through air, surface water, sediment, and land-applied biosolids were evaluated based on fate properties of NMP and screening level analysis. As described in Section 4.6.1.3, EPA did not identify risks to the general population through these pathways. As described in Section 1.4.2, general population exposures through drinking water and disposal are beyond the scope of the risk evaluation. Regarding cumulative exposures, EPA considered the reasonably available information and used the best available science to determine whether to consider aggregate or sentinel exposures for a particular chemical. EPA used PBPK modeling to evaluate total risks from combined inhalation, dermal, and vapor through skin exposures for each COU. EPA concluded that there is insufficient information to support analysis of aggregate exposure across multiple conditions of use. EPA acknowledges that the decision not to aggregate risk across conditions of use could result in an underestimate of risk.
55	**PUBLIC COMMENTS:** • Not considering legacy use, and the risks it poses, disproportionately affects tribes' exposures, in this case due to the unique disposal circumstances on tribal lands and in tribal communities. EPA must consider the impacts of legacy use of NMP on tribal populations.	EPA did not identify, based on reasonably available information, any "legacy uses" or "associated disposals" of NMP, as those terms are described in EPA's Risk Evaluation Rule, 82 FR 33726 (July 20, 2017). Therefore, no such uses or disposals were added to the scope of the risk evaluation for NMP following the issuance of the

		opinion in Safer Chemicals, Healthy Families v. EPA, 943 F.3d 397 (9th Cir. 2019).
55	**PUBLIC COMMENTS:** • Tribes must be considered as a potentially exposed subpopulation under TSCA due to higher consumption of locally caught fish and other aquatic life (*i.e.*, subsistence fishing), substandard housing, lack of worker safety protocols, unique water uses, and other lifeways (*i.e.*, environmental activities for dietary sustenance, socio-cultural activities, ceremonial and spiritual purposes, recreation, and general well-being).	EPA disagrees with public and scientific advisory committee comments on the draft risk evaluation that suggest tribal communities should be identified as PESS. Populations exposed through pathways excluded from the risk evaluation were not identified as PESS. TSCA provides EPA with the discretion to identify the PESS that are relevant to the chemical-specific risk evaluation [TSCA Section 6(b)(4)(A)]. As described in Section 1.4.2, EPA determined that general population exposures through drinking water and disposal pathways are under the jurisdiction of other EPA-administered statutes and fall outside the scope of the risk evaluation. As described in Sections 2.1.1 and 4.6.2, EPA concluded based on first-tier analysis and environmental fate properties considered during problem formulation that general population exposure through ambient air, ambient water, sediment, and land-applied biosolids do not pose a human health risk and did not require further analysis in the risk evaluation. Commenters note that the HBCD risk evaluation identified subsistence fishermen as PESS; however, HBCD is classified as a persistent bioaccumulative toxic (PBT) compound and expected to bioaccumulate through the food chain. NMP is not a PBT and has low bioaccumulation potential. Therefore, NMP is not a significant concern for communities with elevated fish ingestion and the consumption of fish along with other trophic transfer pathways were not included in the scope of the risk evaluation.
55	**PUBLIC COMMENTS:** • Under the SDWA and CWA, multiple tribes use individual groundwater well systems that are not regulated or	As described in the Problem Formulation, EPA did not evaluate risks from NMP exposure through drinking water. Exposures to the general population via drinking water,

	monitored and have members on remote systems that are not POTWs due to the system size.	which includes finished surface and ground water are covered under SDWA. EPA performed an additional analysis of potential exposures through ambient water regulated under the Clean Water Act. While EPA does not have sufficient information about the specific levels of exposure experienced by tribes, the ambient water analysis includes a consideration of potential high-end exposures to NMP through surface water. EPA did not identify risks from incidental ingestion of or dermal contact with NMP in surface water.
55	**PUBLIC COMMENTS:** • Small tribal businesses and self-employed tribal workers are exempt from OSHA, and in rural Alaska non-hub communities, where the majority of Alaska's federally recognized tribes live, OSHA will only provide assistance and compliance visits if three separate entities request them. Most of rural Alaska's communities do not have three entities to which the workplace exposures discussed in the draft risk evaluation would be relevant.	EPA evaluated occupational risk according to exposures and hazards identified through reasonably available information. Risk conclusions do not rely on OSHA standards. EPA considers each condition of use and uses exposure scenarios with and without PPE that may be applicable to particular worker tasks on a case-specific basis for a given chemical. For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on this information and judgement underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in Section 5.2. While EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected. In the case of tribal businesses and/or small business that may not be subject to OSHA regulations, consistency of PPE use is a source of uncertainty in the risk evaluation. In consideration of the uncertainties and

		variabilities in PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determinations in order to address those uncertainties as well as to capture exposures for PESS. EPA has also outlined its PPE assumptions in Section 5.1.
55	**PUBLIC COMMENTS:** • In order to make an accurate risk characterization of tribal communities, EPA needs to consider releases of NMP from landfills as well as any other disposal facility, such as a transfer station or recovery facility.	As described in the Problem Formulation and in Section 1.4.2 of the risk evaluation, EPA did not analyze risks of NMP releases from landfills because they are under the jurisdiction of other statutes. EPA did not include releases to land from RCRA Subtitle D municipal solid waste (MSW) landfills or exposures to the general population from such releases in the risk evaluation. As NMP is not classified as a RCRA hazardous waste, NMP containing solid waste may be sent to RCRA Subtitle D municipal solid waste (MSW) landfills. While permitted and managed by individual states, MSW landfills established after 1989 are required by federal regulations to implement some of the same requirements as Subtitle C landfills. MSW landfills must have a liner system with leachate collection and conduct ground water monitoring and corrective action when releases are detected. MSW landfills are also subject to closure and post-closure care requirements, as well as providing financial assurance for funding of any needed corrective actions. MSW landfills have been designed to allow for the small amounts of hazardous waste generated by households and very small quantity waste generators (< 220 pounds per month). Bulk liquids, such as free solvent, may not be disposed of in MSW landfills. See 40 CFR part 258. NMP containing solid wastes are not expected to be sent to Subtitle C incinerators because NMP is not a hazardous waste and due to higher cost of such incineration as compared with MSW or other incinerators. Emissions from

		hazardous waste incinerators were not evaluated. However, it is possible that NMP containing solid wastes could be sent to subtitle C incinerators due to other characteristics of an NMP-containing solid waste mixture.
55	**PUBLIC COMMENTS:** • It is recommended that "the context of the assessment would be improved by including a graphic" … "that illustrates exposure routes for potentially sensitive or highly exposed populations."	EPA appreciates this suggestion. While EPA is unable to develop this in the timeframe available to complete the NMP risk evaluation, EPA is developing graphics to illustrate potential exposure routes and receptors for future risk evaluations.
Aggregate exposure		
SACC	**SACC COMMENTS:** • Recommendation: Explain the rationale for deciding not to consider risks from combined occupational exposures through multiple tasks. Discuss this decision as a source of uncertainty in the characterization of risk to the population. • Workers may perform multiple work activities within an occupational exposure scenario, especially when sub-scenarios within the use scenario have maximum exposure duration of less than a full shift. This is especially relevant to work activities (sub-scenarios) of short duration in many use scenarios in manufacturing, repackaging, chemical processing-excluding formulation, printing & writing, and recycling & disposal (NMP risk evaluation, Table 2-66).	For most work activities, EPA calculated potential risks based on the assumption that the exposure from that particular work activity is continuous over either a task duration, if available, and portions of a shift, half a shift (for central tendency exposures) or over the whole shift (for high end exposures). While some workers may be exposed to NMP through multiple work activities in a shift, EPA assumes that workers generally perform one activity at a time. The portions of a shift account for multiple contacts, which may be for one or more activities. EPA expects that the risks calculated from a full shift of exposure through single work activities will approximate potential risks for workers who split their shifts across multiple activities that are each performed for shorter durations.
SACC, 51, 55, 34, 48, 61, 46, 59	**SACC COMMENTS:** • Recommendation: Explain the rationale for deciding not to consider aggregate risks from combined occupational and consumer exposure pathways. At a minimum, the implications of not aggregating should be specifically described. Discuss this decision as a source of uncertainty in the characterization of risk to the worker/consumer population. **PUBLIC COMMENTS:**	TSCA Section 6(b)(4)(F)(ii) directs EPA to "describe whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered, and the basis for that consideration" in risk evaluations. EPA defines aggregate exposures as the combined exposures to an individual from a single chemical substance across multiple routes (*i.e.*, dermal, inhalation, or oral) and across multiple pathways (*i.e.*, exposure from different sources). EPA considered the reasonably available information and used the best available science to determine whether to consider

	• EPA considers total exposures within a condition of use but not across conditions of use. EPA must comprehensively evaluate NMP, including all of its conditions of use and how exposures from those uses combine. • EPA should prepare an exposure assessment that examines aggregate exposure. Such an exposure assessment should combine exposures from the inhalation and dermal pathways, including the baseline exposures mentioned above, under all conditions of use. • To fulfill the intent of Congress, EPA must evaluate the true risk of a chemical in commerce, and must therefore consider aggregate and cumulative exposures for all potentially exposed populations (*i.e.*, workers that may also be occupational bystanders and consumers). • That EPA did not combine multiple exposure pathways violates its obligation under TSCA and EPA regulations to use aggregate or sentinel methods of exposure assessment for determinations of unreasonable risk. EPA must justify why it is not employing them. • EPA did not make an overall unreasonable risk determination for NMP but instead made individual risk determinations for dozens of conditions of use. • EPA's final evaluation should base determinations of unreasonable risk on the combined contribution of all conditions of use and pathways to individual NMP exposure.	aggregate or sentinel exposures for a particular chemical. EPA used PBPK modeling to evaluate total risks from combined inhalation, dermal, and vapor through skin exposures for each COU. EPA concluded that there is insufficient information to support analysis of aggregate exposure across multiple conditions of use. EPA acknowledges that the decision not to aggregate risk across conditions of use could result in an underestimate of risk. As stated in Section 4.5, "While this assessment evaluates specific COUs based on exposure estimates that incorporate multiple routes of exposure, it does not consider the potential for aggregate exposures from multiple conditions of use. For example, it does not evaluate the aggregate risk to individuals exposed via occupational and consumer uses. This could result in an underestimate of risk." EPA also identified the lack of aggregate analysis across COUs as a source of uncertainty. As stated in Section 4.3.6, "While the PBPK model allowed EPA to consider aggregate exposure across exposure routes, EPA did not have reasonably available information to consider aggregate exposure across conditions of use. This is a source of uncertainty that may underestimate risk." EPA does not believe exposures need to be integrated for workers with the estimated general population exposures, as the exposures estimated to be experienced by workers are generally significantly higher than general population exposures. Therefore, risk calculated for workers that also accounted for general population or consumer exposure would have minimal to no effect on risk estimates. In accordance with 40 CFR 702.47 "…EPA will determine whether the chemical substance presents an unreasonable risk of injury to health or the environment under each condition of use within the scope of the risk evaluation…". This approach in the implementing regulations for TSCA

		risk evaluations is consistent with statutory text in TSCA Section 6(b)(4)(A), which instructs EPA to conduct risk evaluations to determine whether a chemical substance presents an unreasonable risk "under the condition of use."
Assumptions and uncertainties - General		
SACC, 54	**SACC COMMENTS:** • Recommendation: Describe more appropriately the assumptions and uncertainties in Section 4.3.6 of the draft risk evaluation. • Committee members expressed concerns that Section 4.3.6 Risk Characterization Assumptions and Uncertainties (NMP Risk Evaluation, p. 278) does not reflect appropriately what the title of the section implies. A Committee member suggested that the description of uncertainties in dermal exposure parameters found in section 2.4.1.4. of the draft risk evaluation (pp. 136-137, lines 2864-2884) provides a clear description of sources of uncertainty and could be used as a template for the discussion that summarizes assumptions and uncertainties in the parameters of the risk characterization. **PUBLIC COMMENTS:** • EPA should consider providing a more detailed discussion of uncertainty in the risk characterization section of the revised risk evaluation and quantitatively demonstrate the impacts of alternative plausible approaches on the calculated theoretical risks.	Section 4.3.7 (formerly 4.3.6 as identified by the comment) focuses on assumptions and uncertainties related to the overall integration of exposure and hazard information via the PBPK model. Because specific assumptions and uncertainties vary for each exposure scenario, and uncertainties related to exposure and hazard characterization have been described in previous sections, Section 4.3.7 does not provide the same level of detail as previous discussions of uncertainty. Scenario-specific strengths, limitations, and overall confidence are presented along with risk estimates in Section 4.2.2. To the extent that EPA is able to quantify them, the effect of specific exposure assumptions and parameters on exposure estimates are described in Section 2 and can be further explored in the supplemental risk calculator excel files. Similarly, to the extent that EPA is able to quantify them, the impact of various assumptions and dose-response approaches is described in Section 3.2.6 and can be further explored in the BMD modeling supplemental file. EPA added the new Section 4.3.6 to discuss assumptions and uncertainties associated with the PBPK models.
SACC	**SACC COMMENTS:** • Recommendation: Consider incorporating additional Monte Carlo Analysis and/or sensitivity analysis to better characterize uncertainties. • Characterization of uncertainties could be improved by expanded use of global and specific sensitivity analysis, and	A meaningful Monte Carlo analysis would require information about the variability of specific parameters. For several important sources of uncertainty, EPA lacks the quantitative information that would be needed to inform Monte Carlo analysis. For example, EPA relies on assumptions about specific dermal exposure parameters for

	in some scenarios, Monte Carlo simulations. Several Committee members suggested that Monte Carlo simulations are worthwhile and be used across the board to the greatest extent possible. This approach makes possible: 1) more appropriate characterization of uncertainties due to, for example, polymorphisms and enzyme activity; or 2) make comparisons of risks under different assumptions of PPE use and engineering controls. • Other members of the Committee suggested performing a global and local sensitivity analysis. Performing limited global sensitivity analysis followed by targeted sensitivity analysis of key parameters would accomplish goals like those that could be accomplished using Monte Carlo simulations.	which there is a lack of reliable data. Where possible, EPA has performed sensitivity analysis to characterize the magnitude of uncertainty. For example, where plausible alternate exposure assumptions have been proposed by stakeholders, EPA has considered 'what if' scenarios, to estimate exposure based on alternate industry assumptions. These alternate exposure estimates provide an indication of the magnitude of uncertainty associated with EPA's assumptions. EPA has inserted additional discussion of sensitivity analyses in Section 2. Where possible, EPA describes the magnitude of uncertainty and the potential impact on risk estimates throughout Section 4.3.
SACC	**SACC COMMENTS** • Recommendation: Describe how uncertainties and biases may be increased by creating and using condition of use 'categories' in exposure and hazard assessments and by assigning estimated risks for the 'category' back to the individual scenarios and specific conditions of use. • There is insufficient clarity about how and to what extent uncertainties were considered, weighted, and propagated to arrive at overall confidence about specific risks. For example, decisions made in the process of 'grouping' exposure scenarios and specific conditions of use into 'categories' assumed to have similar exposure and risks, introduces uncertainties and if not performed carefully can lead to biases in exposure and risk estimates. This is particularly a concern when usable exposure measurement data are available for only one or a couple of the specific conditions of use in the condition of use 'category.' The draft risk evaluation is not clear about this potential source of uncertainty and bias and this should be described in more	Risk estimates for each condition of use are based on reasonably available information and there is some uncertainty around the representativeness of these estimates across all exposure scenarios that a relevant for a given COU. EPA provides risk estimates for both central tendency and high end exposures in an effort to capture the range of exposures that may be associated with each condition of use. Where more detailed information is reasonably available, separate risk estimates are shown for several distinct tasks within a given COU (*e.g.*, for lithium ion manufacturing) to provide more specific information to risk managers. In addition, EPA has separated the electronics COU into two distinct COUs (semiconductor manufacturing and other electronics manufacturing). Where more detailed information is not reasonably available, the representativeness of risk estimates for each COU across all facilities and tasks is a source of uncertainty. For occupational exposures, EPA added in Section 2.4.1.4

	detail. Approaches used to account for these potential biases in the final risk characterization need to be presented.	that the application of OESs and associated work activities increases uncertainties in PBPK parameter inputs for OESs that combine COUs and that the directional impacts due to this application of either overestimating or underestimating exposures estimated by PBPK modeling are not known.
Assumptions and uncertainties - Occupational exposure		
SACC	**SACC COMMENTS:** • Recommendation: Clarify the uncertainty introduced by the assumption of similar inhalation exposures for workers and ONUs when estimating the relative contributions from different exposure routes. • Regarding the approach to estimating total human exposures from combined inhalation and dermal exposures using the human PBPK model, the risk evaluation should more clearly explain that this approach assumes the central tendency estimates for inhalation exposures for workers, assigns central tendency PBZ exposures to ONUs, and assumes vapor through the skin exposures are similar for both workers and ONUs. Worker exposure is via inhalation, vapor through skin and dermal liquid contact. ONU exposure is via only inhalation and vapor through skin exposure. • Under these assumptions, the only difference between worker and ONU exposures is the amount of dermal liquid contact of the worker. But if inhalation exposure for workers is actually higher than for ONUs and assuming vapor through the skin exposure estimates are similar, then the difference between worker and ONU exposures now includes both the difference in inhalation exposures and the dermal exposure due to workers' contact with the liquid. This adds uncertainty to the estimate of dermal exposure.	EPA added discussion in Section 2.4.1.1 regarding the relative contributions of each exposure pathway to total exposures, which vary according to parameter values for NMP weight fraction in the liquid product contacted, skin surface areas in contact with the liquid product and with vapor, durations of dermal contact with liquid product and with vapor, air concentration for inhalation and vapor-through-skin exposure, body weight of the exposed person, and glove protection factor and respirator assigned protection factor (if applicable). EPA added clarifications to include the uncertainty of this assumption in the overall confidence discussions at the end of each OES subsection in 2.4.1.2. The uncertainty of this assumption is discussed in Section 2.4.1.4. For most OESs, ONU-specific data and modeling are not available; in these OESs, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA assumed that the workers' central tendency air concentration estimates (rather than the high-end estimates) are appropriate for determining ONUs' air concentration estimates. This assumption does not add uncertainty to the estimate of dermal exposure since it has no impact on dermal exposure.
SACC	**SACC COMMENTS:** • Recommendation: Include a discussion of potential dermal exposures to NMP vapor penetrating through clothing, and	EPA has included discussion in Uncertainties Sections 2.4.1.4 and 4.3 that dermal exposures to NMP vapor that may penetrate clothing fabrics and the potential for

	from contact with NMP vapor-saturated clothing; describe these additional exposure routes as sources of uncertainty in the risk evaluation. • The Committee was concerned about the potential for NMP vapor penetrating through regular (non-impervious fabric) clothing, which could mean that the worker has >25% exposed skin surface area assumed in the draft risk evaluation, which would increase overall skin dermal exposures. • In addition, it is likely that NMP vapor will adsorb/desorb to and from fabric fibers until it equilibrates with airborne NMP levels. This results in contact with NMP-impregnated clothing becoming a source of ongoing dermal exposure throughout the workday.	associated direct skin contact with clothing saturated with NMP vapor are not included in quantifying exposures. The discussion further notes that these uncertainties could potentially result in underestimates of exposures.
SACC	**SACC COMMENTS:** • Recommendation: Include a summary of uncertainties about PPE use.	To the extent that EPA has reasonably available information about PPE use for specific occupational exposure scenarios, it is summarized in Section 2.4.1.2. Throughout Section 4.2.2, in describing the strengths, limitations and overall confidence in risk estimates for each exposure occupational scenario, the risk evaluation describes glove protection factors as assumptions that are a source of uncertainty. Section 4 presents risk estimates for all occupational exposure scenarios for workers both with and without gloves and respirators.
SACC	**SACC COMMENTS:** • Recommendation: Provide a description of the strengths, limitations, and overall confidence for the risk characterization for ONUs (NMP risk evaluation, Section 4.3 and in the summary).	Section 4.2.3 includes a discussion of the overall confidence in risk estimates for ONUs. EPA clarified in 4.2.3 and in all OES subsections of 2.4.1.2 that EPA assigns the same confidence level for PBPK inputs for both workers and ONUs because lower surface areas for liquid contact for ONUs have higher certainty but air concentrations experienced by ONUs have lower certainty. These factors offset one another in determining ONU confidence level using worker confidence level as a starting point.

Assumptions and uncertainties - Consumer Exposure		
SACC	**SACC COMMENTS:** • Recommendation: Emphasize that the CEM assumption that bystanders remain in another room of the household while the consumer uses NMP-containing products adds more differential uncertainty to risk estimates for products that could likely be applied in the presence of a bystander. • The Consumer Exposure Model (CEM) assumes that bystanders remain in one room that is separated from the consumer who is using the NMP-containing product in another room. The draft risk evaluation discussion does not emphasize that this assumption increases the uncertainty of the risk characterization. This assumption may be more appropriate for some products than others. For example, it may not work for an NMP-containing adhesive that can be used in any room of the house, compared to an NMP-containing carbon remover that is typically used only in a more open garage or outdoors.	EPA acknowledges that consumer bystanders were not assumed to be exposed in same room as the users. EPA will consider this refinement to the consumer modeling approach for future evaluations. However, for NMP, a disproportionate route of exposure is dermal from direct handling. Recognizing that the most sensitive receptor for acute exposures is a reproductive-age woman, the risk evaluation assumes such a user and estimates her total (dermal + inhalation) exposure will always exceed any proximate bystander exposure, regardless of their location.
Assumptions and uncertainties - Human health hazard		
SACC, 57, 33	**SACC COMMENTS:** • Recommendation: Add details of the rat inhalation studies as they relate to the total NMP dose (*i.e.*, potential for oral exposure), reproductive stages vis a vis exposure, and the interpretation of maternal and fetal toxicity indicators. • There was insufficient attention to detail in the description of the rodent studies used for risk evaluation. Some of these details (*i.e.*, the potential for additional oral ingestion of NMP by preening, or the developmental stages in rodent studies) could add to uncertainty, but they are not described in the draft risk evaluation as sources of uncertainty. • **PUBLIC COMMENTS:**	EPA agrees that there is uncertainty around NMP doses achieved in whole body inhalation exposure studies. In Section 4.3.5, EPA has inserted additional discussion of the uncertainty around doses achieved in inhalation studies due to aerosolization and potential for oral ingestion due to grooming behavior. This topic is also discussed in Section 3.2.6. The PODs that were ultimately selected as the basis for risk calculations were not reliant on results of inhalation studies. EPA therefore concludes that this source of uncertainty is unlikely to result in an over- or underestimate of risk.

	• It is estimated that the two pathways of vapor-to-dermal and ingestion of vapors would combine to increase the total NMP dose delivered to rats via whole-body exposures by a factor of 3.3-fold compared to vapor inhalation alone. EPA should include quantification of these two pathways (dermal absorption of NMP vapors, ingestion of fur-adsorbed NMP from grooming) when deriving POD values from rat studies for inhalation exposures to NMP. The uncertainties surrounding the potential dermal and oral uptake of NMP, through grooming, in rats following whole-body inhalation should be discussed in Section 4.3 of the risk assessment. At a minimum, this important source of uncertainty should be discussed in Section 4.3 of the risk assessment.	
Risk Conclusions - Risk drivers and overall confidence in conclusions		
SACC	**SACC COMMENTS:** • Recommendation: Indicate clearly the main driver(s) for the risk estimates for each of the specific conditions of use. Provide a more transparent justification for the overall levels of confidence presented in the summaries. • The exposures, MOEs, and risk estimates need to be examined carefully to ensure findings make sense across the specific conditions of use and occupational exposure scenarios in each condition of use category, acknowledging the limits on the data that were available to derive the estimates. A clearer justification is needed for the overall level of confidence for each specific risk estimate. • It is not clear how limitations, strengths, and assessed uncertainties translate into assigned low, medium, or high levels of confidence. More information is needed, and the decision process better defined, on how limitations and strengths in risk estimates are considered and weighed in assigning overall confidence to risk estimates. Some Committee members suggested that quality scores could be	In the risk evaluation the main drivers for risk estimates were identified in the unreasonable risk determination for each condition of use. In the determinations in which unreasonable risk was found, the term "unreasonable risk driver" was used to label the risk drivers, and in determinations where no unreasonable risk was found, the exposure scenario with the highest risk estimate was described. EPA thanks the SACC commenters for their recommendations and has revised the risk evaluation to add clarity on this issue. EPA added discussion in Section 2.4.1.1 regarding the relative contributions of each exposure pathway to total occupational exposures, which vary according to parameter values for NMP weight fraction in the liquid product contacted, skin surface areas in contact with the liquid product and with vapor, durations of dermal contact with liquid product and with vapor, air concentration for inhalation and vapor-through-skin exposure, body weight of

	used, for example, when there is conflicting information, such as in the toxicology data. In addition, qualifiers should be removed from the risk evaluation when describing uncertainty (*e.g.,* "some uncertainty"). Numerical values should be provided when uncertainties are quantifiable, and or when describing levels of exposure (*e.g.,* add the percentile in addition to indicating "high end").	the exposed person, and glove protection factor and respirator assigned protection factor (if applicable). In scenarios where the three parameters involving dermal contact with liquid product (NMP weight fraction in the liquid product contacted, skin surface areas in contact with the liquid product and with vapor, durations of dermal contact with liquid product) have relatively high values, this route can be the dominant route for worker exposures. EPA assigned low, medium or high levels of overall confidence qualitatively based on consideration of the specific limitations, strengths, and uncertainties identified for each exposure scenario and the hazard points of departure.
SACC	**SACC COMMENTS:** • Recommendation: Remove qualifiers that do not provide meaningful information when describing uncertainties and provide numerical values whenever possible in conclusions about level of confidence. • There was discussion about the description of risk as "not unreasonable" instead of just saying "reasonable" or considering the term "measurable risk."	EPA has revised the language describing uncertainties to avoid unnecessary qualifiers. For many aspects of uncertainty and confidence, EPA lacks sufficient information to provide numerical values, but EPA has provided quantitative information where possible.
SACC	**SACC COMMENTS:** • Recommendation: Address more specifically how uncertainties impact MOEs when making "no unreasonable risk" determinations and increase MOEs to accommodate uncertainty. • There are uncertainties in the toxicity assessment and the PBPK model. The extent of uncertainties appears too high to support with confidence a determination of no unreasonable risk. • The risk evaluation should only support "no unreasonable risk" determinations when and where more solid evidence is available, and uncertainties are judged to be truly small.	Section 5 of the risk evaluation describes how uncertainties impact the determinations of unreasonable or no unreasonable risk. The degree of uncertainty surrounding the MOEs, cancer risk or RQs is a factor in determining whether or not unreasonable risk is present. Where uncertainty is low, and EPA has high confidence in the hazard and exposure characterizations (for example, the basis for the characterizations is measured or monitoring data or a robust model and the hazards identified for risk estimation are relevant for conditions of use), the Agency has a higher degree of confidence in its risk determination. EPA may also consider other risk factors, such as severity

	Where uncertainties are large, MOEs need to be larger as well, to reflect those larger uncertainties.	of endpoint, reversibility of effect, or exposure-related considerations, such as magnitude or number of exposures, in determining whether the risks are unreasonable under the conditions of use.
SACC	**SACC COMMENTS:** • Recommendation: Provide a discussion of strengths, weaknesses, and overall confidence for characterization of risk to environmental receptors, following the pattern of these descriptions for risks to human health (Sections 4.3.5 and 4.3.6).	Additional discussion has been added to Sections 4.1.2 and 4.3.4 of the final risk evaluation to discuss the strengths and weaknesses of the environmental hazard and risk characterization as well as identify the main sources of uncertainty.
Risk conclusions – Other		
34, 51	**PUBLIC COMMENTS:** • EPA repeatedly finds that risks that fall below the benchmark MOE or that exceed EPA's cancer threshold are reasonable, and need not be managed under TSCA. • In its final risk evaluation, EPA should adhere to its own unreasonable risk criteria and not reclassify risks that meet these criteria as "reasonable."	A calculated MOE for non-cancer risk that is less than the benchmark MOE indicates the possibility of unreasonable risk to human health. Whether there are unreasonable risks will depend upon other risk-related factors, such as severity of endpoint, reversibility of effect, exposure-related considerations (*e.g.*, duration, magnitude, frequency of exposure, population exposed), and the confidence in the information used to inform the hazard and exposure values. If the calculated MOE is greater than the benchmark MOE, generally it is less likely that there is unreasonable risk.
61, 51, 53	**PUBLIC COMMENTS:** • While EPA's draft risk evaluations find that certain uses of NMP pose unreasonable risks, EPA understates those risks and thus violates TSCA's mandate to protect workers. • EPA miscalculates the severity of worker risks by misconstruing OSHA requirements related to the use of respirators and other PPE. • EPA has significantly understated NMP's risks because of several omissions, indefensible assumptions and errors in its risk evaluation methodology…Of most concern is EPA's assumption that millions of exposed workers are "expected" to wear protective gloves	In Sections 2 and 4, the risk evaluation presents exposure and risk estimates for each occupational exposure scenario both with and without glove use. To the extent that EPA has reasonably available information about glove use in a specific industry, it is described in Section 2.4.1.2. In Section 4.2.2, EPA acknowledges that glove protection factors for each exposure scenario are a source of uncertainty for exposure and risk estimates. For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on information and judgement underlying the exposure scenarios. These

	• It is requested that EPA reach a conclusion of unreasonable risk of injury to worker health, from chronic inhalation and dermal exposure during drum unloading and loading into shipping containers	assumptions are described in the unreasonable risk determination for each condition of use, in Section 5. Additionally, in consideration of the uncertainties and variabilities in PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determinations in order to address those uncertainties. EPA has also outlined its PPE assumptions in Section 5.1. EPA agrees that there are challenges associated with use of PPE; they are described in Section 5. By providing risk estimates with use of PPE, EPA is not recommending or requiring use of PPE. Rather, these risk estimates are part of EPA's approach for developing exposure assessments for workers that use the reasonably available information and expert judgment. When appropriate, in the risk evaluation, EPA will use exposure scenarios both with and without engineering controls and/or PPE that may be applicable to particular worker tasks on a case-specific basis for a given chemical. While EPA has evaluated worker risk with and without PPE, it would be unrealistic for EPA to assume that workers are typically unprotected by PPE.
56	**PUBLIC COMMENTS:** • EPA's draft finding of unreasonable risk for workers during lithium ion cell manufacturing is based on erroneous assumptions concerning how our industry handles NMP, implements engineering controls, and protects workers.	Thank you for the comment. EPA worked with the lithium ion cell manufacturing industry to incorporate substantiated information into the Final Risk Evaluation. EPA revised the occupational exposure assessment in the risk evaluation to separately assess occupational exposure scenarios associated with three categories of electronic part manufacturing: Lithium ion battery manufacturing (2.4.1.2.15); Other electronics manufacturing, including capacitor, resistor, coil, transformer, and other inductor manufacturing (2.4.1.2.9); and Semiconductor manufacturing (2.4.1.2.10). In these separate OESs, EPA revised and expanded PBPK runs for industry-specific work

		activities using industry-specific air concentration data sets provided in public comments for the lithium ion battery manufacturing industry, for the semiconductor manufacturing industry, and from the OSHA data set for capacitor, resistor, coil, transformer, and other inductor manufacturing (LICM, 2020a; Semiconductor Industry Association, 2020, 2019b, c; OSHA, 2017).
52, 64	**PUBLIC COMMENTS:** • For purposes of the final risk evaluation, EPA must consider the specific conditions of NMP use in the semiconductor industry separately from other sectors with which they were combined for purposes of the draft risk evaluation. • The Agency must update and enhance its final risk assessment, and conclude, pursuant to 40 CFR Section 702.49(d) of EPA's risk evaluation rules, that the use of NMP in the semiconductor industry does not present an unreasonable risk. Moreover, EPA should determine that the conditions of use in the sector require no further regulatory scrutiny under Section 6 of TSCA.	Thank you for the comment. EPA worked with the semiconductor industry to incorporate documented assumptions and information into the Final Risk Evaluation. EPA revised the occupational exposure assessment in the risk evaluation to separately assess occupational exposure scenarios associated with three categories of electronic part manufacturing: Lithium ion battery manufacturing (2.4.1.2.15); Other electronics manufacturing, including capacitor, resistor, coil, transformer, and other inductor manufacturing (2.4.1.2.9); and Semiconductor manufacturing (2.4.1.2.10). In these separate OESs, EPA revised and expanded PBPK runs for industry-specific work activities using industry-specific air concentration data sets provided in public comments for the lithium ion battery manufacturing industry and for the semiconductor manufacturing industry, and from the OSHA data set for capacitor, resistor, coil, transformer, and other inductor manufacturing (SIA, 2019b, c; SIA, 2020; LICM, 2020b; OSHA, 2017).
53	**PUBLIC COMMENTS:** • The high-end scenario may not represent actual exposure in the workplace. EPA used monitoring data to develop an 8-hour TWA for the high-end exposure scenario. Modeling for this high-end scenario indicates that exposure does not meet MOE threshold, indicating unreasonable risk. The 8-hour period does not reflect actual exposure times of a worker	EPA differentiates between worker contact duration with liquid and inhalation duration in Section 2.4.1.1 and explains that PBPK inputs are adjusted to normalize these durations.

	during a shift. As a result, the conclusion of unreasonable risk does not necessarily mean that workers are exposed to a health risk in the workplace.	
Adherence to TSCA – Effects on determination of risk		
46, 56	**PUBLIC COMMENTS:** • The draft conclusions in this risk evaluation should not be allowed to stand, consistent with TSCA, where best available science has not been used.	EPA risk conclusions are based on best available science and the weight of the scientific evidence.
51	**PUBLIC COMMENTS:** • The NMP draft risk evaluation is incomplete and inadequate and does not comply with TSCA in the absence of sufficient data to address whether all endpoints present an unreasonable risk of injury. EPA's failure to develop risk estimates for developmental neurotoxicity, immunotoxicity, and endocrine effects is effectively a recognition that it cannot make unreasonable risk determinations under TSCA Section 6(b) for these endpoints using currently available data.	EPA evaluated the reasonably available information from animal toxicology studies. While EPA agrees that there is limited information for some endpoints, EPA considers the database adequate for risk evaluation without the need to separately address immune effects on their own. In Section 3.2.6 and Section 4.3.5, EPA identifies the limited data for developmental neurotoxicity, immunotoxicity and endocrine effects as sources of uncertainty that could result in an underestimate of risk.
59	**PUBLIC COMMENTS:** • EPA has failed to acknowledge that the requirements it relies on derive from statutes (*e.g.*, OSHA) that establish criteria different than those under TSCA for establishing requirements to address human and environmental health risks. Many of these other statutes, for example, require EPA or other agencies to consider factors such as cost and feasibility when setting standards – factors that TSCA explicitly forbids EPA from taking into account when assessing risks.	EPA risk conclusions are based on exposure and hazard characterization that EPA performed based on reasonably available information. EPA evaluated exposure and hazard without consideration of costs or other non-risk factors, and without using other statutory risk assessment standards that consider cost or non-risk factors. While EPA assumed PPE use for some conditions of use based on the assumption of compliance with OSHA standards, the risk associated with a given level of exposure is based on EPA's independent evaluation of reasonably available information.
Risk mitigation/management		
53	**PUBLIC COMMENTS:** • EPA should use actual workplace exposure data or exposure times for each conditions of use or recognize the limitations of its approach when considering risk mitigation measures.	EPA uses all reasonably available actual workplace exposure data for each condition of use. For duration of dermal contact with liquids, EPA did not find reasonably available actual workplace exposure durations and explains

		assumptions as noted in Section 2.4.1.1. EPA explains the uncertainties of these assumptions in Section 2.4.1.4.
53, 31	**PUBLIC COMMENTS:** • Since EPA will initiate risk mitigation in summer 2020, it is recommended that EPA consider requiring PPE where it has issued a finding of no unreasonable risk based on use of PPE. • EPA should recognize limitations during risk mitigation so as not to prescribe unnecessarily restrictive and unjustified control measures, including banning NMP or setting unreasonable *de minimis* values for the uses described. • As a result of lower exposure potential from significant operational control, risk mitigation criteria should be specific and less rigorous for semiconductor manufacturing. • There is concern that EPA will not be able to prescribe adequate risk mitigation measures tailored to a condition of use because of inconsistencies and vaguely supported findings. • EPA can assist businesses by requiring PPE that mitigates risk to "no unreasonable risk."	Thank you for the comment. For any conditions of use found to present unreasonable risk in the final risk evaluation, EPA will move immediately into risk management. EPA will consider any comments related to risk management at that time. EPA evaluated all conditions of use of NMP under TSCA, including commercial and industrial uses that result in occupational exposures. Risk management activities are outside the scope of the risk evaluation. As the commenter indicated, as appropriate for any condition of use determined to present unreasonable risk, EPA will consider feasibility in implementation of any risk management actions that are proposed to address the unreasonable risks that EPA has determined are presented. In that context, EPA intends to analyze the applicability of any PPE training, certification, and limited access programs.
53	**PUBLIC COMMENTS:** • EPA's finding of unreasonable risk will be used to develop risk mitigation measures after EPA finalizes its risk evaluation in summer 2020. Yet, for several conditions of use, EPA has not identified, to a high degree of certainty, conditions causing risk. • There is concern that EPA's draft risk evaluation will identify issues for further examination without clearly identifying conditions leading to unreasonable risk to workers and consumers. This in turn might result in EPA developing unnecessary or flawed risk mitigation measures.	Thank you for the comment. Per the statute (see TSCA Section 6(b)(4)(A)) and the implementing regulations for risk evaluations (40 CFR part 702, subpart B), EPA must make the unreasonable risk determination at the time of the risk evaluation. Upon finding unreasonable risk, EPA will apply risk management actions to the extent necessary so that the chemical no longer presents such risk, in accordance with TSCA Section 6(a). For any conditions of use found to present unreasonable risk in the final risk evaluation, EPA will move immediately into risk management. EPA will consider any comments related to risk management at that time. EPA evaluated all conditions of use of NMP under TSCA, including commercial and

		industrial uses that result in occupational exposures. Risk management activities are outside the scope of the risk evaluation. As the commenter indicated, as appropriate for any condition of use determined to have unreasonable risk, EPA will consider feasibility and implementation of any risk management actions that are proposed to address the unreasonable risks that EPA has determined are presented.
61	**PUBLIC COMMENTS:** • By assuming extensive use of PPE at the risk evaluation stage, EPA conflates risk evaluation with risk management. • PPE is a risk management tool, albeit a poor one that may be used only when preferable options are not available. As such, PPE may only be considered, if at all, during the risk management stage when it can be weighed against more effective means of risk reduction.	Thank you for the comment. EPA has updated Table 2-77 to include worker exposures for all glove PFs for all OESs. A hierarchy of controls is a method for eliminating workplace hazards. While EPA has assessed the extent to which certain exposure reduction tools that it assumes to be in place may be reducing risks to workers, application of the methodology of the hierarchy of controls is not relevant to risk evaluations. EPA will manage unreasonable risks presented by chemical substances when the Agency undertakes regulatory action for COUs determined to have unreasonable risk. Utilization of the hierarchy of controls to recommend or require risk management actions in the risk evaluation would be premature and inappropriate. A hierarchy of controls is a method for eliminating workplace hazards. While EPA has assessed the extent to which certain exposure reduction tools that it assumes to be in place may be reducing risks to workers, application of the methodology of the hierarchy of controls is not relevant to risk evaluations. EPA will manage unreasonable risks presented by chemical substances when the Agency undertakes regulatory action for COUs determined to have unreasonable risk. Utilization of the hierarchy of controls to recommend or require risk management actions in the risk evaluation would be premature and inappropriate.
38, 48, 51, 61	**PUBLIC COMMENTS:** • EPA should immediately move forward to finalize a ban on	EPA appreciates the comment. As published in the Methylene Chloride rule for consumer paint and coating

	paint stripping uses as proposed in 2017.	removal, "EPA intends to incorporate NMP use in paint and coating removal in the risk evaluation for NMP. EPA has concluded that the Agency's assessment of the potential risks from this widely used chemical will be more robust if the potential risks from these conditions of use are evaluated by applying standards and guidance under amended TSCA. In particular, this includes ensuring the evaluation is consistent with the scientific standards in Section 26 of TSCA, including using best available science and systematic review approaches." EPA evaluated all conditions of use of NMP under TSCA, including commercial and industrial uses that result in occupational exposures. Risk management activities are outside the scope of the risk evaluation. As stated in the executive summary of the risk evaluation, any proposed or final determination that a chemical substance presents unreasonable risk under TSCA Section 6(b) is not the same as a finding that a chemical substance is "imminently hazardous" under TSCA Section 7.
32, 54	**PUBLIC COMMENTS:** • EPA should revisit the clarity and organization of Table 5-1. It is difficult to understand. EPA should boldface both the "presents" and the "does not present" statements in Table 5-1 to improve its risk communication about its risk determinations. • In addition, EPA's "presents" and "does not present" statements should cite to the Section 26 statutory and regulatory requirements demonstrating that the determinations are based upon best available science, weight of the scientific evidence, and data quality. • A statement regarding the uncertainty in the appropriate dose metric and outcome response rate for resorptions should be added to the table.	Thank you for the comment. EPA added clarity to Table 5-1 and the risk determination language in Section 5 in the final risk evaluation.

	• EPA should consider including a modified table that represents the relevant endpoints and drivers, potentially color-coding those that exceed benchmarks.	

8. Content and Organization

Content and Organization		
Charge Question 7.1: Please comment on the overall content, organization, and presentation of the NMP draft risk evaluation. Please provide suggestions for improving the clarity of the information presented. **Charge Question 7.2:** Please comment on the objectivity of the underlying data used to support the risk characterization and the sensitivity of the agency's conclusions to analytic assumptions made.		
#	**Summary of Comments for Specific Issues Related to Charge Question 7**	**EPA Response**
Evaluation scope, methodology, and transparency		
SACC, 46, 51, 55, 46	**SACC COMMENTS:** • Recommendation: Document and distribute to the public a clear description of the following: o The rationale for focusing TSCA evaluations only on exposures to occupational users, non-occupational users, and direct consumers of chemical-containing products to the exclusion of exposures to the broader public. [Note: the conditions of use discussion in Section 1.4 is inadequate for this purpose.] o The timeline for combining risk assessments conducted under TSCA, CAA, and CWA regulations to produce a complete picture of risks from TSCA listed chemicals. o The rationale and approach for making "unreasonable risk" determinations under TSCA. [Section 5.1.1 of the NMP draft risk evaluation has a good discussion of this but does not address the PPE use issue that keeps arising in Committee discussions.] • Readers of TSCA-focused evaluations receive only a partial picture of risks to the chemical being assessed. • The Committee continues to express its concern that	EPA has added Section 1.4.2, which describes exposure pathways and risks that fall under the jurisdiction of other EPA-administered statutes or regulatory programs. As described in Section 1.4.2, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA believes that coordinated action on exposure pathways and risks addressed by other EPA-administered statutes and regulatory programs is consistent with statutory text and legislative history, particularly as they pertain to TSCA's function as a "gap-filling" statute, and also furthers EPA aims to efficiently use Agency resources, avoid duplicating efforts taken pursuant to other Agency programs, and meet the statutory deadline for completing risk evaluations. EPA has therefore tailored the scope of the risk evaluation for NMP using authorities in TSCA Sections 6(b) and 9(b)(1). As described in Section 4.6.2.3, some exposure pathways that are not covered under other statutes were considered during problem formulation, but not further analyzed in the risk evaluation. During problem formulation, EPA evaluated potentials exposures and risks to the general population through

	this incomplete picture of risks may be used to promote improper releases and disposal of chemicals that may harm not only worker and ONU health, but also the health of the general population. • The Committee encourages the Agency to rapidly complete the assessment of all other releases and general population exposures and associated hazard to complete the risk picture for NMP. **PUBLIC COMMENTS:** • EPA's draft risk evaluation excludes all human exposures from environmental releases of NMP, resulting in the absence of any consideration of environmental pathways that contribute to overall human risk exposure and risk. This approach is an unlawful interpretation of TSCA, has twice been rejected by the SACC, and overlooks the widespread presence of NMP in environmental media to which millions of people are exposed. • The air, water, and waste pathways excluded from the NMP draft risk evaluation are significant contributors to human exposure and should be included in risk determinations. • EPA cannot evaluate, as it purports to do here, the total, cumulative risk to public health and the environment from these chemicals if it excludes exposures through other pathways.	ambient water, land-applied biosolids, and ambient air. Based on environmental fate properties of NMP and first-tier screening level analyses, EPA did not identify risk to the general population from these pathways. In the final risk evaluation, EPA included an updated analysis of potential risks from incidental ingestion and dermal contact with NMP in surface water based on more recent TRI data. EPA concluded that there is insufficient information to support analysis of aggregate exposure across multiple conditions of use for NMP. EPA acknowledges that the decision not to aggregate risk across conditions of use could result in an underestimate of risk.
Other data to consider		
SACC	**SACC COMMENTS:** • One Committee member suggested studies (Babich et al., 2004, Van Engelen et al., 2008) that provide better information on children's mouthing behavior of toys.	EPA has included these references in the final risk evaluation.
SACC	**SACC COMMENTS:**	EPA held several meetings with States to gather chemical data including a call specifically with Washington State Department

	• Several Committee members reiterated that EPA should pursue additional data on use and use practices from states (Washington, Vermont, Maine, and Oregon) having chemical use permitting laws that require reporting of these practices for targeted chemicals. The Committee recognizes that such reports may represent content or concentrations only (rather than fully inform exposure) and are subject to significant over-reporting rather than being based on experimental data.	of Ecology in January 2017. EPA also routinely highlighted NMP and the other "First 10 Chemicals" in meetings with the Environmental Council of States (ECOS) and other EPA quarterly calls on toxic chemicals. EPA held several public comment periods encouraging the submittal of chemical use information. EPA carefully considered the best approach to capture the conditions of use across and within sectors using NMP, and relied on communications with companies, industry groups, environmental organizations and public comments to supplement the use information. EPA had sufficient information to complete the NMP risk evaluation using a weight of the scientific evidence approach. EPA selected the first 10 chemicals for risk evaluation based in part on its assessment that these chemicals could be assessed without the need for regulatory information collection or development. When preparing this risk evaluation, EPA obtained and considered reasonably available information, defined as information that EPA possesses, or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation. In some cases, when information available to EPA was limited, the Agency relied on models; the use of modeled data is in line with EPA's final Risk Evaluation Rule and EPA's risk assessment guidelines. However, EPA will continue to improve on its method and data collection for the next round of chemicals to be assessed under TSCA.
Editorial - Clarity/transparency		
SACC	**SACC COMMENTS:** • EPA should use a standard format for citations, ensuring that primary original data sources are cited and reviewed (not simply subsequent papers or sources using the original data), and including a sentence or	EPA has made revisions throughout the risk evaluation to cite original sources and clarifying where only secondary sources are available.

	two stating the salient point when referencing supporting documents.	
SACC	**SACC COMMENTS:** • One Committee member suggested that using color in tables to highlight significant findings rather than simply bolding values would improve clarity of findings.	To improve clarity, EPA has modified table formatting to shade cells to highlight significant findings (in addition to bolding values).
SACC	**SACC COMMENTS:** • SACC reported a number of editorial corrections to be addressed in the revised risk evaluation.	EPA appreciates this feedback and has made editorial revisions where possible to improve clarity.
31	**PUBLIC COMMENTS:** Clarification/increased transparency is requested for the following: • The basis for the Agency's handling of air sampling data with observations falling below detection limits is not transparent. EPA should provide a record of the values used for the LOD in the Agency's statistical adjustments. • EPA's statistical analysis when interpreting air sampling results cannot be reproduced based on the limited information provided. More details about the PBPK model and its inputs are needed. • On page 176 of the Supplemental Information on Occupational Exposure Assessment, why are line items 19 & 20 excluded? Is there confusion about the name of the sample called "Fab Area samples?"	The Supplemental Information on Occupational Exposure Assessment describes in Section 1.4.3.1 how EPA handles datasets with results below detection limits. Specifically, for datasets including exposure data that were reported as below the limit of detection (LOD), EPA estimated the exposure concentrations for these data, following EPA's *Guidelines for Statistical Analysis of Occupational Exposure Data* (U.S. EPA, 1994). which recommends using the $\frac{LOD}{\sqrt{2}}$ if the geometric standard deviation of the data is less than 3.0 and $\frac{LOD}{2}$ if the geometric standard deviation is 3.0 or greater. Additional information on how EPA used datasets containing results below detection limits for specific OES was included in the appropriate subsections of the Supplemental Information on Occupational Exposure Assessment (Section 2.8 Electronics Parts Manufacturing and Section 2.9 Printing and Writing). Line items 19 & 20 of page 176 of the Supplemental Information on Occupational Exposure Assessment were incorrectly labeled as personal breathing zone samples. This was corrected to area samples. These data were excluded because EPA used personal breathing zone monitoring data,

		which is higher on the hierarchy in selecting data and approaches for estimating air concentrations.
59	**PUBLIC COMMENTS:** • EPA has not provided public access to at least 12 sources that include health and safety information on which EPA relies in its draft risk evaluation. • While they have entries in EPA's Heath and Environmental Research Online (HERO) database, those entries do not provide a means of accessing the documents themselves. While some of the reference list entries cite OTS, TSCATS, and other cross-references, our searches for these failed to yield access to the information sources. • While EPA claims not to have relied on two of these studies, conflicting language elsewhere in the draft risk evaluation requires clarification from EPA.	EPA appreciates this comment and generally expects to make the information it uses for decision-making publicly available, consistent with and subject to the requirements of TSCA Section 14. The commenter identified several specific references. EPA addressed access to each study as follows: • 4 studies by BASF (2001, 1989, 1986, 1983) ○ 1983: Acute fish toxicity ○ 1986: Acute fish toxicity ○ 1989: Acute algae toxicity ○ 2001: Chronic aquatic invertebrates These are unpublished aquatic toxicity studies in the HERO database. • DTI (2004): Survey of chemical substance in consumer products. EPA is working to upload the document into HERO. • Dupont (1990). A HERO link provided for this study in the draft risk evaluation linked to the wrong Dupont 1990 document. The link has been corrected in the final risk evaluation. While the DuPont 1990 study is not publicly available, it is consistently cited in tandem with Solomon, 1995, the publicly available version of the same study which was published in the peer reviewed literature and is publicly available. The data EPA relied on is publicly available through Solomon, 1995 and the Dupont 1990 citation is provided for reference and to be clear that both references refer to the same study. • Huntingdon (1998). The information provided in this dermal exposure study in rats indicates that certain solvents can increase permeability of NMP. While EPA cites this study

		for context, EPA does not have sufficient information about each exposure scenario to incorporate solvent-specific permeability estimates. The information in this study provides useful context but does not provide the quantitative analysis performed by EPA. • NMP Producers Group (1999a, b). EPA did not have access to these two generation reproduction studies at the time the draft risk evaluation was released. EPA has since obtained access to both studies and posted them to the docket with names of some study personnel redacted. • Prestige (2010): Safety data sheet. The link to this SDS appears to have become broken. In HERO, EPA replaced the broken link with a link to the product web page and added a PDF of the SDS as it appeared when it was originally found. • SIA (2019c): These exposure monitoring results are available in the public docket.
59	**PUBLIC COMMENTS:** • In the draft risk evaluation, EPA stated that the NMP Producers Group studies "contribute to overall weight of evidence." However, an apparently contradictory statement indicates that EPA did not use the results of these studies in its analysis. • EPA needs to clarify that the studies will not be used in its "overall weight of evidence" approach unless the full studies are provided to EPA and made public along with providing an opportunity for public comment on them.	In the draft risk evaluation, EPA did not have access to either of the NMP Producers Group two-generation reproductive toxicity studies. EPA has since obtained access to both studies and posted them to the docket [EPA-HQ-OPPT-2019-0236]. EPA evaluated both studies using the systematic review data quality criteria, performed dose-response analysis for developmental endpoints reported in the studies, and incorporated results of the studies into hazard identification, weight of the scientific evidence and dose-response analysis.
54	**PUBLIC COMMENTS:** • EPA should more clearly explain its approach to analyzing the potential risks of substances that are already subject to other federal environmental programs. EPA should also consider whether its	As described above, EPA has inserted Section 1.4.2, which describes exposure pathways and risks that fall under the jurisdiction of other EPA-administered statutes or regulatory programs. EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have

	approach is consistent across its TSCA risk evaluations, and if not, to explain why not.	expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the scope of the risk evaluation for NMP using authorities in TSCA Sections 6(b) and 9(b)(1).
Editorial - Accuracy		
31	**PUBLIC COMMENTS:** Comments on accuracy of the Supplemental Information on Occupational Exposure Assessment: • The semiconductor manufacturing industry does not use any open top tanks of NMP; the actual process in the semiconductor industry is VERY different than that described, and therefore, the descriptions are not accurate. • The following statement is incorrect "data received from European Semiconductor Industry (SIA) 2019." The word "European" should be removed. • The high number of Semiconductor and Other Electronic Component Manufacturing listed in Table 2-39 is incorrect. • Based on process descriptions provided earlier in this document, the last sentence on page 81 is not correct. Semiconductor manufacturing has more controlled NMP handling practices than other electronics parts manufacturing. • The following statement is incorrect: "EPA did not find data on exposure duration." SIA provided exposure duration for each task and samples were taken for duration of exposure. • Table 2-42 contains some information considered to be inaccurate: No one in semiconductor manufacturing handles containers for 6-12 hours/day; several of the tasks in this table are also not completed on a daily	EPA revised the process description in Section 2.8.1 (Electronics Manufacturing) of the Supplemental Information on Occupational Exposure Assessment. Specifically, EPA included a process description specifically for semiconductor manufacturing alone, which does not include the use of open top tanks. EPA made the suggested revision to remove "European" from "data received from European Semiconductor Industry (SIA) 2019." EPA revised Section 2.8.2.2 to include separate estimates of number of sites and workers for each electronics manufacturing OES. This revision resulted in fewer sites and workers specifically applicable to semiconductor manufacturing. EPA revised the occupational exposure assessment in the risk evaluation to separately assess occupational exposure scenarios associated with three categories of electronic part manufacturing: Lithium ion battery manufacturing (2.4.1.2.15); Other electronics manufacturing, including capacitor, resistor, coil, transformer, and other inductor manufacturing (2.4.1.2.9); and semiconductor manufacturing (2.4.1.2.10). In these separate OESs, EPA revised and expanded PBPK runs for industry-specific work activities using industry-specific air concentration data sets provided in public comments for the lithium ion battery manufacturing industry and for the semiconductor

	basis; and exposed skin surface area values do not align with the percentage of exposed skin that SIA provided when discussing the PPE used to handle NMP. • On page 86, Section 2.8.4, the summary statement seems inaccurate for the amount of data SIA provided, most of which yielded non-detect results. • Regarding the statement on page 172, "However, no other methods to address the reporting limit of detection exist (EPA, 1994)," it was suggested that EPA use the AIHA method defined in A Strategy for Assessing and Managing Occupational Exposures and the accompanying spreadsheet IHSTAT.	manufacturing industry, and from the OSHA data set for capacitor, resistor, coil, transformer, and other inductor manufacturing (LICM, 2020a; Semiconductor Industry Association, 2020, 2019b, c; OSHA, 2017). Therefore, semiconductor manufacturing is no longer assumed to be representative of all subcategories of the Electronic Part Manufacturing OES, and the sentence that had been at the bottom of page 81 was deleted. EPA replaced the statement "EPA did not find data on exposure duration" with "EPA did not find reasonably available data on actual duration of dermal contact with liquids." EPA also revised PBPK inputs for this OES to include "what-if" task duration-based durations for liquid contact, which use tasks durations provided from public comments, including from SIA public comments (Semiconductor Industry Association, 2020, 2019b, c). While EPA revised the assessment to include "what-if" task duration-based PBPK inputs when available, EPA retains full-shift and half-shift shift-based duration PBPK inputs for all OESs due to uncertainty of task durations representing actual durations of contact with liquids. EPA revised the statement from page 86, Section 2.8.4, of the draft risk evaluation to include a third exposure route, vapor-through-skin exposure. The new sentence is in Section 2.9.4 due to reorganizing of sections. The presence of a fraction, even a majority, of non-detect values of air concentrations does not remove the potential for exposure through any of these routes. EPA deleted the statement from the draft risk evaluation on page 172, "However, no other methods to address the reporting

		limit of detection exist (EPA, 1994)." However, EPA retained the approach used (U.S. EPA, 1994) because it is consistent with EPA's approach in other current chemical risk evaluations.
59	**PUBLIC COMMENTS:** • EPA's descriptions of its glove use assumptions and analysis are contradictory within the text and are inconsistent with the information that it relied on in its risk estimates table (Table 4-50) and risk determination table (Table 5-1).	In the risk characterization in Section 4, EPA presents risk estimates for all occupational COUs both with and without PPE. In the risk determination in Section 5, EPA makes unreasonable risk determinations based on risk estimates and reasonably available information on PPE use for each COU. EPA has outlined the PPE assumptions in Section 5.1 and EPA's assumptions are described in the unreasonable risk determination for each condition of use, in Section 5.2.
57	**PUBLIC COMMENTS:** • In Table 3-3-1 of the BMD supplemental file, the number of litters cited in the table for the 120 and 831 mg/L dose groups differs from the values used in the BMD modeling and should be corrected.	This was an error. EPA has updated the number of litters from 21 to 22 for the 120 mg/L dose group, and from 5 to 25 for the 831 mg/L dose group to match the number of litters reported in the original Saillenfait, et al. (2002) publication. The updated litter sizes appear in Table 2-2 of the updated BMD Supplemental file.
Editorial - Suggested additions		
SACC	**SACC COMMENTS:** • Recommendation: Consider adding a comprehensive table/appendix for each occupational use scenario, sub-scenario, and scenario characteristic (central tendency or high-end) that, in addition to the information provided in Table 2-66, also includes all of the acute and chronic non-cancer risk estimates. This may be helpful to industrial hygienists as they consider how task duration, NMP concentration, hand exposure, and PPE use modify risk.	In Section 2.4.1.3, EPA stated that the full range of this modeling is presented in the spreadsheet Supplemental File on Occupational Risk Calculations. This file covers all of the aspects that are indicated in this comment.
SACC	**SACC COMMENTS:** • One Committee member suggested that a map of facilities that use NMP or discharge NMP could be helpful, especially in providing connections between use, disposal, human health, and the environment. It	EPA thanks the Committee member for the suggestion to add a map of facilities that use or discharge NMP. EPA will give consideration to the feasibility of adding facility mapping to future TSCA chemical risk evaluations, which will be weighed against any security concerns.

	was acknowledged that there are potential security issues in producing such a map.	
SACC	**SACC COMMENTS:** • One Committee member thought it would be helpful if EPA was clear on which references in Table 1-5 actually include (NMP risk evaluation, p. 31, lines 481-2) "information on conditions of use, hazards, exposures and potentially exposed or susceptible subpopulations," and where and how that information was used in the risk evaluation.	EPA appreciates this suggestion. While this is not possible in the time available to complete the NMP risk evaluation, EPA will consider such a table for future risk evaluations.
SACC	**SACC COMMENTS:** • One Committee member suggested that a fact sheet on dermal parameters should be a standard part of each TSCA chemical risk evaluation. This fact sheet should both include theoretical values and specifically provide ranges based on physical-chemical properties and experimental results where data are available in the research literature.	EPA will consider this type of communication material for future risk evaluations. Dermal exposure parameters are described in the risk evaluation in Section 2.4.1.1, 2.4.2.3, and 3.2.5.5. Details of scenario-specific assumptions in occupational exposure scenarios are available throughout Section 2.4.1 and in the supplemental file *Supplemental Information on Occupational Exposure Assessment*.
Systematic review - Limitations of guidelines studies		
38	**PUBLIC COMMENTS:** • According to the TSCA Systematic Review, higher quality studies are guideline studies or data collected according to GLP requirements. Guideline studies are most often designed to identify major toxic effects (apical effects) like cancer, major organ weight gain or loss, body weight gain or loss, skeletal malformations, and clinical signs; they are not sufficiently sensitive to reliably identify low-dose exposure, endocrine of hormonal effects, or neurobehavioral effects that may occur at low doses during critical windows of development. • The TSCA Systematic Review guidelines result in inappropriate favoring of industry studies, without	The TSCA risk evaluation strategies in some cases refer to study guidelines along with professional judgement as helpful guidance in determining the adequacy or appropriateness of certain study designs or analytical methods. This should not be construed to imply that academic research studies or other non-guideline studies are automatically given lower confidence ratings than guideline or Good Laboratory Practice (GLP) studies typically conducted by industry. EPA considers reasonably available, relevant data and information that conform to the TSCA science standards when developing the risk evaluations irrespective of whether they were conducted in accordance with standardized methods (*e.g.*, OECD test guidelines or GLP standards).

	assessing study quality. Studies conducted by industry, as well as academic research studies, should be systematically evaluated using a credible Systematic Review method, such as used by the EPA Integrated Risk Information System (IRIS) program and the National Institute of Environmental Health Sciences.	EPA will publish a protocol document for the next TSCA risk evaluations. To refine that protocol, EPA is reviewing existing peer-reviewed systematic review approaches, consulting with EPA's IRIS program, and considering feedback from the NASEM TSCA Committee.
Systematic review - Information from ECHA dossiers		
59	**PUBLIC COMMENTS:** • On p. 47 of its draft risk evaluation, EPA claims that ECHA dossiers are existing chemical assessments equivalent to EPA and Agency for Toxic Substances and Disease Registry (ATSDR) governmental assessments. • ECHA dossiers are not assessments and are not government documents. They are compilations of industry information submitted to ECHA that have not been evaluated for quality or reliability by ECHA or any other governmental entity. For EPA to equate them with EPA and ATSDR assessments is simply wrong. o At the bottom of each page of each dossier is a statement that the information has not been reviewed or verified by ECHA or any other authority. While some chemicals do eventually undergo a "substance evaluation" by government authorities under REACH, NMP has not. o EPA exacerbates the mischaracterization through its text references to the industry's dossiers, typically cited as "ECHA, [date]." Clicking on that link takes the reader to EPA's entry for that source in its HERO data system, in which the reference's author is prominently listed as the "European Chemicals Agency." Such text citations and HERO entries are misleading. All of these	Industry submitted ECHA dossiers have not gone through the same level of review as government assessments. EPA removed the reference to ECHA dossiers in the footnote offering examples of previous assessments. Where possible, EPA now cites original sources rather than summaries in ECHA dossiers.

	documents were prepared by the industry registrants, not ECHA.	
59	**PUBLIC COMMENTS:** • EPA does not have access to the full studies for all of the studies on which it relies in the draft risk evaluation. The ECHA dossiers EPA has cited contain only summaries of studies, not the studies themselves. Even the best study summaries are incomplete descriptions that do not allow for an independent examination of study quality and conclusions reached by authors. • Systematic review practices require access to full studies, as details of study design and results are necessary elements of consistently determining study quality and ultimately evidence integration. • EPA needs to not only obtain copies of the full studies, but also make full copies of all studies on which it relies available to the public. • EPA needs to review the full study reports to confirm that the information in the summaries meets the scientific standards set forth in TSCA section 26. Without access to full studies, EPA and the public will be challenged or unable to assess and comment on the quality of the studies.	EPA has obtained and reviewed reasonably available genotoxicity studies using the systematic review data quality criteria. However, some of the studies cited and summarized in ECHA dossiers are not available to EPA. Where possible, EPA has revised citations to refer to primary sources that are publicly available rather than relying on secondary sources. EPA's conclusions are based on data reasonably available from primary sources. In some places, EPA notes the existence of additional studies summarized in dossiers but for which EPA does not have access to the full study. References to these study summaries are only included to provide a complete picture of reasonable available information, not to serve as the basis for EPA decisions.
59	**PUBLIC COMMENTS:** • In the scoring sheet for the summary of the first of the three degradation studies, EPA repeatedly noted it is a "secondary source" that provides limited detail and that the "primary source may have more detail." It is not clear what the "primary source" actually is, and EPA appears to rely on the industry-prepared summary instead of the primary source. The lack of important	EPA has replaced the ECHA study summaries by their respective primary sources: Shaver, (1984) for the first, Gerike and Fischer (1979) and Křížek et al. (2015) for the second, and U.S. EPA (2012) (*i.e.*, EPI Suite™) for the third.

	detail in the summary also calls into serious question the medium ranking EPA assigned to it. • In the scoring sheet for the summary of the second of the studies, EPA repeatedly refers to information that was "not reported" or was "omitted." In a few places, EPA adds without citing any basis that such omissions "did not limit the interpretation of the results" or "were not likely to have had a substantial impact on the study results." It is exceedingly difficult to understand how EPA can possibly draw such conclusions in the absence of access to the full study (which is unpublished). Nor are such flaws consistent with the "high" quality ranking EPA assigned to the study. With the study itself not made available, the public is left with no ability to independently assess the validity of such statements or EPA's reliance on the summary in the draft risk evaluation. • The third study is apparently not an experimental study but an estimation based on a quantitative structure-activity relationship (QSAR) software model that EPA developed. It is not at all clear why EPA did not run in its own model rather than rely on an industry-prepared summary of its run of the same model. Moreover, in the summary in the ECHA dossier, the industry registrant notes several major caveats regarding its reliability. These statements by the industry registrant are wholly at odds with EPA's assignment of a "high" quality ranking, but these summaries were still used in its analysis.	
Systematic review – General		
40	**PUBLIC COMMENTS:**	EPA published the *Strategy for Conducting Literature Searches for NMP: Supplemental Document to the TSCA Scope Document* in 2017 along with the scope document for NMP.

	• The protocol for the TSCA systematic review process was not provided in the draft risk evaluation and does not follow the general steps for a systematic review. • The TSCA method excludes the following steps: protocol development, evidence identification, evidence integration, and hazard identification. In addition, the TSCA method uses a non-empirically based 'scoring' system, includes metrics inside each domain not relevant to study quality, and excludes relevant studies.	This document outlined the literature search strategy and title/abstract inclusion/exclusion criteria used for screening. EPA subsequently published *Application of Systematic Review in TSCA Risk Evaluations* that described the data quality criteria used for each discipline and outlined data integration strategies that will be further developed for the next risk evaluations. Because the systematic review steps have been published and are available to the public, EPA did not publish the protocols in the risk evaluation documents. EPA/OPPT's quality evaluation method was developed following identification and review of various published qualitative and quantitative scoring systems to inform our own fit-for-purpose tool. The development process involved reviewing various evaluation tools/frameworks (*e.g.*, OHAT Risk of Bias tool, CRED, etc.; see Appendix A of the Application of Systematic Review in TSCA Risk Evaluations document and references therein), as well as soliciting input from scientists based on their expert knowledge about evaluating various data/information sources specifically for risk assessment.
51	**PUBLIC COMMENTS:** • The TSCA approach applies a rigid scoring system to grade the "quality" of studies on chemicals. This system could result in many studies being arbitrarily classified as "poor" or "unacceptable" based on a small number of reporting or methodology limitations that do not negate their overall value for assessing health and environmental risks. The consequence will be that important evidence of public health impacts will be either disregarded or given limited weight in risk evaluations. • The updated criteria make it more difficult for epidemiological studies to be scored as high quality,	EPA has comprehensively evaluated the reasonably available human and animal studies for NMP. The epidemiologic criteria were revised to more stringently distinguish between High, Medium and Low studies. After additional piloting of the criteria, EPA found that the initial iteration of the epidemiological data quality criteria (as published in the Application of Systematic Review in TSCA Risk Evaluations) was inadvertently skewing quality scores toward the tail ends of the scoring spectrum (High and Unacceptable). In order for the criteria to represent a more accurate depiction of the quality levels of the epi literature, the criteria were revised. With the changes to the criteria, EPA observed fewer studies with Unacceptable ratings and more

	reflecting a consistent tendency by the TSCA program to downplay the value of human evidence.	studies shifting from High to Medium, with only the highest quality studies receiving a High overall rating. EPA is in the process of revising the data quality criteria for future assessments based on feedback from the NASEM TSCA Committee.
34, 40, 51, 53	**PUBLIC COMMENTS:** • In EPA's "hierarchy of preferences," EPA does not explain why some types of studies should receive preference over others and on what basis these studies should be assigned to a "higher level." • This hierarchy of preferences is not peer reviewed or part of any documents on which EPA took public comment. • There are no objective criteria for determining which evidence to rely on and which to exclude, undermining transparency and consistency and encouraging subjective judgments. • The hierarchy of preferences was used to exclude 39 relevant and acceptable sources. In the draft risk evaluation, EPA recognizes that the quality of data in excluded studies is acceptable for risk assessment. These studies were not identified or made public. • EPA should make excluded studies available or, at a minimum, provide a list of excluded studies with an explanation of how EPA applies its hierarchy of preferences	Different lines of evidence are routinely used in TSCA chemical assessments because of data availability, sources, underlying documentation, and quality varies. EPA preferentially relies on a variety of test and analog data. In the absence of suitable test data, predictive modeling tools may be used. EPA clarified under Figure 1-6 that lower quality data from 39 sources were not integrated based on EPA's integration approach (*i.e.*, higher quality data from other sources were used; in these cases, the hierarchy of preferences was not a factor in the decision). EPA also added that the data integration approach for releases and occupational exposure data is discussed in Appendix C of the document titled Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1 Methyl-) (NMP), Supplemental Information on Occupational Exposure Assessment (U.S. EPA, 2019b). EPA will seek peer review of its Systematic Review protocol, including the hierarchy of approaches to exposure estimation.
53	**PUBLIC COMMENTS:** • There is concern that EPA may continue to inadvertently exclude useful information from review in future risk evaluations. This problem is compounded by unclear review criteria that change due to the iterative nature of data collection and screening.	The timeframe for development of the TSCA Scope documents was very compressed and the first ten chemical substances were not subject to prioritization, the process through which EPA expects to collect and screen much of the relevant information about chemical substances. As a result, EPA had limited ability to develop a protocol upfront. For these reasons, the protocol development was staged in phases while conducting the

	• While EPA has provided general inclusion criteria in Appendix G of the NMP Problem Formulation, EPA has not provided information on how it applies these criteria to exclude relevant studies. EPA also states that that application of review criteria is subject to change with each risk evaluation.	assessment work (see Section 3.1 of the Application of Systematic Review in TSCA Risk Evaluations for more discussion of this step). EPA is in the process of revising the data quality criteria for future assessments based on feedback from the NASEM TSCA Committee. EPA published the literature search strategy and title/abstract inclusion/exclusion criteria for NMP in the *Strategy for Conducting Literature Searches for NMP: Supplemental Document to the TSCA Scope Document*. EPA will publish a protocol document for the next TSCA risk evaluations. Furthermore, EPA has received feedback from the NASEM TSCA Committee on its systematic review process and will carefully review their recommendations for future chemicals.
34, 48	**PUBLIC COMMENTS:** • The TSCA systematic review method is not evidence-based, lacks transparency, is not peer reviewed, and is likely to have resulted in a biased evidence base for the risk evaluation. Inadequate methods were used to assess risk of bias, including financial conflicts of interest. The method relies on numerical scores that falsely imply a relationship between scores and effect or association.	EPA/OPPT's quality evaluation method was developed following identification and review of various published qualitative and quantitative scoring systems to inform our own fit-for-purpose tool. The development process involved reviewing various evaluation tools/frameworks (*e.g.*, OHAT Risk of Bias tool, CRED, etc.; see Appendix A of the Application of Systematic Review in TSCA Risk Evaluations document and references therein), as well as soliciting input from scientists based on their expert knowledge about evaluating various data/information sources specifically for risk assessment. EPA will publish a protocol document for the next TSCA risk evaluations. Furthermore, EPA has received feedback from the NASEM TSCA Committee on its systematic review process and will carefully review their recommendations for future chemicals.
48	**PUBLIC COMMENTS:**	EPA has revised its searching and screening procedures to include all studies in the systematic review process (screening,

	• EPA states that it "leveraged information presented in previous assessments when identifying relevant key and supporting data." The supplemental documents do not contain the phrasing "key and supporting information." There has been, and continues to be, a lack of clarity on how EPA chose and evaluated the key sources. EPA should define what "key and supporting" information is.	data evaluation) for the next set of TSCA chemical risk evaluations. In other words, no key and supporting studies will bypass any step in the systematic review process. EPA defines key and supporting data in a footnote in Section 1.5.1, "Key and supporting data and information are those that support key analyses, arguments, and/or conclusions in the risk evaluation."
40, 34, 48, 51, 53	**PUBLIC COMMENTS:** • Suggestions for improving the systematic review process include: ○ Detailed documentation and transparency of how information was identified and evaluated. ○ Follow best practices in the field to simplify the data quality criteria and to synthesize and integrate each evidence stream. ○ Do not be overly stringent and exclude studies based on a single criterion. ○ Submit the process for review to the NAS. ○ Develop a protocol prior to commencing the systematic review. ○ Consider using an existing peer-reviewed method such as the that used by the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction, the Institute of Medicine, or EPA's IRIS program.	EPA will publish a protocol document for the next TSCA risk evaluations. To refine that protocol, EPA is reviewing existing peer-reviewed systematic review approaches, consulting with EPA's IRIS program, and considering feedback from the NASEM TSCA Committee.
Systematic review - Evidence integration		
48	**PUBLIC COMMENTS:** • It is recommended that EPA conduct separate evidence synthesis and determinations about the certainty of the evidence for each stream of evidence and describe how different streams of evidence are integrated to draw conclusions.	When synthesizing and integrating evidence for each human health hazard endpoint, EPA considered quality, consistency, relevancy, coherence and biological plausibility as specified in *Application of Systematic Review in TSCA Risk Evaluations*. For NMP, EPA considered each of these factors qualitatively in characterizing the weight of the scientific evidence and overall

		confidence in selected PODs. The weight of the scientific evidence for hazard endpoints is described Section 3.1.3. The rationale for selection of specific PODs is described in Section 3.2.5.6 and the strengths and weakness and overall confidence in each POD are described qualitatively in Section 3.2.6.
Transparency of citations - General handling of CBI data		
59, 54	**PUBLIC COMMENTS:** • Under TSCA Section 14(b)(2)(A), the law's restrictions on disclosure of CBI do not apply to "any health and safety study which is submitted under this Act" for a chemical substance that "has been offered for commercial distribution." Therefore, any information reported to or obtained by EPA from a health and safety study must also be disclosed. • The regulations are explicit that tests to determine the chemical and physical properties and fate and transport behavior of a substance fall within the definition, along with studies of a chemical's human health effects and ecotoxicity and assessments of human and environmental exposure, 40 CFR § 720.3(k). • EPA should exercise its discretion to protect CBI in Health and Safety studies authorized under TSCA by appropriately balancing the competing interests of transparency and protection of compensability. Information that would qualify for protection includes the submitter's identity, the identities of employees who worked on the study, and confidential commercial information in the study (*e.g.,* financial statistics, product codes, information that discloses processes used in the manufacture or processing of the chemical, or the portion of a chemical in a mixture); information needed for regulatory acceptance where	The key and supporting studies EPA relied on as the basis for quantitative analysis in the final risk evaluation are publicly available. At the time of the draft risk evaluation, several studies were not available to EPA. These studies were therefore cited but not used as the basis for quantitative analysis. EPA has since received two two-generation reproduction studies from NMP Producers Group. EPA posted these studies to the public docket, evaluated study quality using the systematic data quality criteria, and incorporated relevant information from the studies into the weight of the scientific evidence considered in hazard characterization and dose-response analysis. Where possible, EPA revised citations to refer to primary sources that are publicly available rather than relying on secondary sources. EPA's conclusions are based on data reasonably available from primary sources. In some places, EPA notes the existence of additional studies cited and summarized in dossiers, but these are only included to provide a complete picture of reasonably available information, not to serve as the basis for EPA decisions.

	compensability (commercial value) of the study may be an issue.	
54	**PUBLIC COMMENTS:** • Section 26 clearly contemplates that not all information relevant to a Section 6 risk evaluation will be publicly available. "Subject to Section 14" means that Congress contemplated that CBI contained in information relied upon to support a scientific decision by the agency may not be subject to disclosure. Section 26(j)(4) requires that EPA identify the "list of studies considered" in a risk evaluation along with their results, but not that the entire studies themselves would necessarily be made public. The practical effect of EPA's decision not to use the two NMP producers' more recent studies was to forego its obligations under Section 26 to use the best available science and apply the weight of the scientific evidence.	EPA thanks the commenter for their input. EPA has added additional studies to docket # EPA-HQ-OPPT-2019-0236 available at www.regulations.gov. Releasing these studies ensures EPA's risk evaluation process is transparent, robust, and uses the best available science. EPA received these studies after publishing the draft NMP risk evaluation.
59	**PUBLIC COMMENTS:** • EPA appears to have appropriately rejected relying on the missing sources submitted by the NMP Producer's Group because the agency correctly determined that the health and safety studies could not be claimed CBI, as requested by the submitter, and indicated that it could not rely on these studies if it did not make them public. • For 10 sources from the NMP Producer's Group, EPA has not described any claim(s) of confidentiality that it believes justifies withholding them. These information sources are all "health and safety studies" that cannot receive CBI protection under TSCA. • EPA's obligation to disclose these references cannot be satisfied merely by releasing "robust	EPA appreciates the comment. EPA remains committed to a transparent and reproducible systematic review process to ensure that the information the Agency relies on in its risk evaluations meets the scientific requirements in TSCA Section 26. EPA has emphasized that in order to evaluate the quality of a study, the Agency needs access to the complete study methodology and a complete set of data tables and summary statistics for all endpoints. Without this information, EPA does not have a basis to judge the quality of a study through our TSCA systematic review process or to assess the conclusions by applying a weight of the scientific evidence approach. Since the release of the draft risk evaluation, EPA received the NMP Producers' Group studies and has added the studies to docket # EPA-HQ-OPPT-2019-0236 available at https://www.regulations.gov/. Releasing these studies ensures EPA's risk evaluation process is transparent, robust, and uses the best available science. EPA

	summaries" but requires public access to the full studies.	received these studies after publishing the draft NMP risk evaluation in November 2019. These studies from the NMP Producers Group provide the agency with additional information on developmental and reproductive toxicity.
54	**PUBLIC COMMENTS:** • Although EPA claims the NMP Producers Group proposed options that would make the CBI publicly available in a restricted manner (*e.g.*, in a reading room not subject to mechanical reproduction), EPA rejected them for reasons that are not persuasive. • EPA states that deviating from the practice of making information available in the dockets "may create a vulnerability for the Agency now, and in the future, in its implementation of TSCA section 6." • EPA's protestations are unpersuasive in light of the well-established importance CBI has for U.S. companies and the U.S. economy. Precedence exists for EPA's use of restricted-access reading rooms in other comparable circumstances. • For example, amendments to the RMP statutory authority in CAA § 112(r) allow public access, through reading rooms, to paper copies of offsite consequence analysis information. • Possible solutions for handling CBI: If EPA posts unredacted studies on its website, study owners may lose the compensation value for use of those studies in other jurisdictions to which they would otherwise be entitled. This can result in substantial harm to their competitive positions. The potential loss of compensability also leads to reluctance to submit studies voluntarily, such as in this instance with the NMP draft risk evaluation. Options that EPA can employ to address this issue include:	EPA seeks to establish a transparent and reproducible systematic review process to ensure that the information the Agency relies on in its risk evaluations meets the scientific requirement in TSCA Section 26. In order to evaluate a study's quality, EPA needs access to the complete study methodology and a complete set of data tables and summary statistics for all endpoints. Without this information, EPA does not have a basis to judge the quality of a study through our TSCA systematic review process or to assess the conclusions by applying a weight of the scientific evidence approach. Since the release of the draft risk evaluation, EPA received the NMP Producers' Group studies and has added the studies to docket #EPA-HQ-OPPT-2019-0236 available at www.regulations.gov.

	○ Confidentiality agreements: Any stakeholder willing to sign a confidentiality agreement would receive a full copy of the study, including any CBI redacted from the public version of the study. ○ Public reading rooms: Unredacted paper copies of studies could be made available in EPA public reading rooms, as long as they could not be mechanically duplicated. ○ Voluntary submissions: EPA has a strong interest in voluntary submission of studies on Section 6 chemicals, even if there is not complete public disclosure of the studies. Whether or not companies that own studies choose to make them available to EPA depends in part on whether or not EPA will make the studies public in a manner that results in loss of compensability. • Where EPA lacks statutory authority to require submission of studies on Section 6 chemicals, as with European companies preparing REACH dossiers, EPA has no alternative but to accept studies with redactions designed to preserve compensability. Even where EPA has statutory authority to require submission of studies on Section 6 chemicals, EPA should prefer to receive the studies without having to exercise that statutory authority.	
Transparency of citations – NMP Producers Group 1999 studies		
33, 54	**PUBLIC COMMENTS:** • The NMP Producers Group sponsored two reproductive toxicity studies to help clarify the findings from Exxon (1991), the key study for derivation of PODs for reproductive effects. • The NMP Producers Group was agreeable to providing full study reports to EPA but requested that they not be	At the time the draft risk evaluation was released, EPA did not have access to unredacted versions of either of the NMP Producers Group 1999 studies. NMP Producers Group was initially hesitant to share the studies if they were to be made public. NMP Producers Group has since provided unredacted versions of both studies to the agency. EPA has reviewed the studies using the systematic review data quality criteria,

	publicly posted and that they be protected as CBI. EPA did not respond to the Group's request and rejected this proposal as insufficient for reasons that were not clearly explained. • EPA did not explain in the draft risk evaluation why it does not have complete access to the full reports. Is it possible that EPA made an unnecessarily restrictive interpretation of TSCA Section 14?	integrated results into hazard identification, weight of the scientific evidence, and dose-response analysis, and posted the studies to the public docket. EPA generally expects to make the information it uses for decision-making publicly available, consistent with and subject to the requirements of TSCA Section 14.
General feedback on TSCA risk evaluations for existing chemicals		
54	**PUBLIC COMMENTS:** • EPA should convene a broader discussion with other EPA program offices about how OPPT should coordinate with the other EPA program offices on how OPPT should address substances already specifically regulated by these other offices, as well as substances that EPA addresses through more general regulatory requirements. • EPA should articulate the principles and approaches that will form the foundation of EPA's intra-agency coordination efforts and provide the public the opportunity to comment.	EPA communicated with other program offices within the agency throughout the risk evaluation process, including at scoping, problem formulation, and both draft and final risk evaluation. These discussions included regulatory requirements and processes of the various environmental statutes. EPA will continue to have these conversations with other offices at the Agency for the next round of chemicals to be evaluated under TSCA Section 6. See Section 1.4.2 of the risk evaluation regarding EPA's approach to exposure pathways and risks addressed by other EPA-administered statutes. In the 2017 Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act (82 FR 33726, July 20, 2017), EPA committed to, by codifying, interagency collaboration to give the public confidence that EPA will work with other agencies to gain appropriate information on chemical substances. This is an ongoing deliberative process and EPA is not obligated to provide descriptions of predecisional and deliberative discussions or consultations with other federal agencies. In the interest of continuing to have open and candid discussions with our interagency partners, EPA is not intending to include the content of those discussions in the risk evaluation.
34, 53, 31, 32	**PUBLIC COMMENTS:** • SACC meetings should not be scheduled before the close of the comment period on the draft risk	EPA appreciates the comment and will consider whether a longer comment period is warranted for future draft risk evaluations. EPA did extend the public comment period for the

	evaluations. This limits the information available to the SACC, depriving the Committee of the benefit of comments that could have enabled a more focused and informed review. • The current tight public comment deadlines compromise stakeholder's ability to comment. A thorough review of the draft risk evaluation was not possible. • The final deadline for submission of public comments should be extended in the future by an additional 30 days – to 90 days – at least through the next round of 20 high priority chemicals.	draft risk evaluation of NMP by two additional weeks to give stakeholders more time to review and comment on the draft document.
SACC	**SACC COMMENTS:** • It was suggested that representatives from OSHA and NIOSH attend these evaluation reviews to help answer questions that the Committee continues to have on issues related to occupational safety and health.	OSHA and NIOSH were able to comment on this document during interagency review. EPA will consider adding representatives from OSHA or NIOSH attend future peer review meetings.
SACC	**SACC COMMENTS:** • Recommendation: Consider including GHS classification information on the subject chemical. • The GHS classification is the primary mechanism for communicating hazards of a chemical in an industrial setting through SDSs and labeling. The GHS provides a way to compare relative hazards across substances and could provide useful context to readers.	EPA appreciates this suggestion and will consider this approach for future risk evaluations.
38	**PUBLIC COMMENTS:** • An important Expert Consensus Statement published in Nature Reviews Endocrinology earlier this year identifies 10 "key characteristics of endocrine-disrupting chemicals as a basis for hazard identification." The EPA TSCA program could gain much benefit from incorporating these current	Thank you for recommending this resource.

	scientific approaches into its chemical risk evaluations, including NMP.	
38	**PUBLIC COMMENTS:** • EPA should consider utilizing mechanistic data when evaluating chemicals and should incorporate these current scientific approaches into its chemical risk evaluations.	In response to this comment, EPA has further explored mechanistic evidence for NMP. While there is very limited mechanistic data available for NMP, EPA has identified some evidence that NMP is a bromodomain inhibitor. This suggests a plausible mechanism for male reproductive effects. Additional discussion of this mechanistic evidence has been added to Section 3.2.4.2. The mechanistic studies supporting this discussion were evaluated using the systematic review data quality criteria. EPA is in the process of modifying the systematic review approach to incorporate mechanistic data earlier in the risk evaluation process. Future risk evaluations may be supported by available mechanistic data identified through systematic review.
39	**PUBLIC COMMENTS:** • There are some fundamental flaws in the Simon et al. (2016) implementation of Bayesian/probabilistic methods. • If adopting a Bayesian approach, it is recommended that EPA adopt the WHO/IPCS (2017b) framework in its probabilistic analysis. Numerous tools are available for implementing it, including an Excel spreadsheet tool APROBA available on the WHO website (WHO/IPCS, 2017a), an RShiny web app APROBAweb (Chiu, 2018), and as part of the Bayesian Benchmark Dose online web system, benchmarkdose.org (Shao and Shapiro, 2018).	EPA must incorporate all reasonably available information, defined in 40 CFR 702.33 as "information that EPA possesses or can reasonably generate, obtain, and synthesize for use in risk evaluations, considering the deadlines specified in TSCA Section 6(b)(4)(G) for completing such evaluation." Due to time and resource constraints associated with the deadline for completing the NMP risk evaluation, EPA cannot implement a Bayesian framework comprehensively for this risk evaluation as the information is not reasonably available; however, EPA will consider incorporating more probabilistic modeling into future risk evaluations under TSCA.
54	**PUBLIC COMMENTS:** • There are several risk assessment models that EPA might use to communicate its TSCA risk characterizations, such as HESI's Risk21 Project and Web Tool. EPA should consider this approach, or a	EPA will investigate the methods and principles behind the HESI Risk 21 application and consider using its visualizations in future risk evaluations.

	similar approach that provides an effective visual representation of the potential range of risks, to aid in communication of the risk characterization for the conditions of use.	
SACC	**SACC COMMENTS:** • One Committee member suggested providing a section to the document that clearly explains the public health implications (not benefits) of the overall findings. This could be a standard part of the executive summary or a stand-alone statement. For example, the summary for NMP could highlight that dermal exposure from direct skin contact and from vapor-to-skin contributes the largest fraction of dose compared to exposure via inhalation. • In addition, the summary could review the extent of exposures (geographically and via population numbers) and provide estimated numbers of occupationally exposed workers in some of the most affected occupations.	EPA appreciates the comment and will consider including additional information where feasible in future risk evaluations. It should be noted that Table 2-4 "Estimated Number of Workers in the Assessed Industry Uses of NMP" provides estimates by occupational exposure scenario of the number of workers potentially exposed in manufacturing, chemical processing and other occupational scenarios.
53	**PUBLIC COMMENTS:** • At the SACC meeting, the SACC and EPA considered stopping SACC's review of each draft evaluation so it only convenes occasionally to discuss issues of emerging science that could affect how EPA conducts evaluations. • The SACC should continue to conduct review of each draft risk evaluation at least through the next group of 20 TSCA risk evaluation chemicals. • EPA may need to further adjust its approach to risk evaluations to consider aggregated effects and legacy uses.	EPA appreciates these comments and will consider this input for future risk evaluations. Regarding aggregate exposures, TSCA Section 6(b)(4)(F)(ii) directs EPA to "describe whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered, and the basis for that consideration" in risk evaluations. EPA defines aggregate exposures as the combined exposures to an individual from a single chemical substance across multiple routes (*i.e.*, dermal, inhalation, or oral) and across multiple pathways (*i.e.*, exposure from different sources). 40 CFR 702.33. EPA considers the reasonably available information and used the best available science to determine whether to consider aggregate or sentinel exposures for a particular chemical.

	• The SACC's continued input on these and other matters, through review of each draft risk evaluation, would assist EPA in establishing a consistent approach.	

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