EPA SCIENTIFIC ADVISORY COMMITTEE ON CHEMICALS
CHARGE TO THE PANEL – N-METHYLPYRROLIDONE

As amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act on June 22, 2016, the Toxic Substances Control Act (TSCA), requires the U.S. Environmental Protection Agency (EPA) to conduct risk evaluations on existing chemicals. In December of 2016, EPA published a list of the initial ten chemical substances that are the subject of the Agency's chemical risk evaluation process (81 FR 91927), as required by TSCA. N-Methylpyrrolidone (NMP) is one of the first ten chemical substances and the fifth of the ten to undergo a peer review by the Scientific Advisory Committee on Chemicals (SACC). In response to this requirement, EPA has prepared and published a draft risk evaluation for NMP. EPA has solicited comments from the public on the draft and will incorporate them as appropriate, along with comments from the peer reviewers, into the final risk evaluation.

The focus of this meeting is to conduct the peer review of the Agency's draft risk evaluation of NMP and associated supplemental materials. At the end of the peer review process, EPA will use the reviewers' comments/recommendations, as well as the public comments, to finalize the NMP draft risk evaluation.

This draft risk evaluation contains the following components:

- Discussion of chemistry and physical-chemical properties
- Characterization of uses/sources
- Environmental fate and transport assessment
- Environmental exposure assessment
- Human health hazard assessment
- Environmental hazard assessment
- Risk characterization
- Risk determination
- Detailed description of the systematic review process developed by the Office of Pollution Prevention and Toxics to search, screen, and evaluate scientific literature for use in the risk evaluation process.

CHARGE QUESTIONS:

Systematic Review (Section 1.5 of the Draft Risk Evaluation):

The Toxic Substances Control Act (TSCA) requires that EPA use data and/or information in a manner consistent with the "best available science" and that EPA base decisions on the "weight of the scientific evidence". The EPA's Final Rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726), defines ''best available science'' as science that is reliable and unbiased. This involves the use of supporting studies conducted in accordance with sound and objective science practices, including, when available, peer reviewed science and supporting studies and data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data). The Final Rule also defines the "weight of the scientific evidence" as a systematic

review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including the strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.

To meet these scientific standards, EPA applied systematic review approaches and methods to support the NMP draft risk evaluation. Information on the approaches and/or methods is described in the draft risk evaluation as well as the following documents:

- *Strategy for Conducting Literature Searches for NMP: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0743)
- *NMP (CASRN 872-50-4) Bibliography: Supplemental File for the TSCA Scope Document*, (EPA-HQ-OPPT-2016-0743)
- *N-Methylpyrrolidone Problem Formulation* (EPA-HQ-OPPT-2016-0743)
- *Application of Systematic Review in TSCA Risk Evaluations*

EPA has solicited peer review and public feedback on systematic review approaches and methods for prior evaluations. A general question on these approaches is not included in this charge; however, EPA will accept comment on the systematic review approaches used for this evaluation if provided.

1. Environmental Fate and Exposure (Sections 2.1 and 2.2 of the Draft Risk Evaluation):

The environmental fate of NMP is characterized by partitioning to the atmosphere, surface water and groundwater, and degradation by atmospheric oxidation or biodegradation. It is not expected to persist in the environment and has a low bioaccumulation potential. EPA did not further analyze the environmental fate of NMP as indicated by the conceptual models in the problem formulation.

1.1 Please comment on the data, approaches and/or methods used to characterize exposure to aquatic receptors.

2. Environmental Hazard and Risk Characterization (Sections 3.1 and 4.1 of the Draft Risk Evaluation)

A screening-level analysis of potential risk to aquatic species indicates that expected environmental concentrations are below hazard thresholds for aquatic species. In addition, a qualitative consideration of physical-chemical properties and the conditions of use in this assessment indicate that risks to sediment-dwelling invertebrate species and terrestrial species are not expected.

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

(Section 3.1) and the findings outlined in the draft risk characterization section (Section 4.1).

3. Exposure and Releases (Section 2.4 of the Draft Risk Evaluation):

Workers and occupational non-users may be exposed to NMP when performing activities associated with conditions of use including, but not limited to:

- Unloading and transferring NMP to and from storage containers to process vessels;
- Using NMP in process equipment (e.g., applying photoresists during silicon wafer production);
- Applying formulations and products containing NMP onto substrates (e.g., applying adhesives, sealants and NMP-containing products that facilitate their removal);
- Cleaning and maintaining equipment;
- Sampling chemical formulations or products containing NMP for quality control
- Repackaging chemical formulations or products containing NMP
- Handling, transporting and disposing wastes containing NMP;
- Performing other work activities in or near areas where NMP is used.

3.1 Please comment on the reasonableness of the characterization of occupational exposure for workers and occupational non-users. What other additional information, if any, should be considered?

EPA distinguishes between workers (users) and occupational non-users (ONUs) to acknowledge that different tasks and activities are associated with different levels of exposures and thus risk in the same workplace. EPA assumes that area air monitoring is an appropriate surrogate for ONUs exposure. In the absence of ambient air monitoring data, EPA assumes that the central tendency of personal breathing zone (PBZ) monitoring data is a good surrogate for ONU exposures because the agency rarely has PBZ monitoring data for ONUs. EPA also uses probabilistic modeling approaches where available for conditions of use. In these cases where EPA uses modeling of near field and far field zones we assume the working use is in the near field zone and the ONUs are in the far field zone.

3.2 Please comment on the transparency of EPAs approach and the assumptions EPA used to characterize exposure for ONUs.

Workplace exposure PBPK modeling inputs were developed for adults using NMP or formulations containing NMP. EPA found limited published data for NMP air concentrations in workplace settings during use of NMP or formulations containing NMP. These data were used as inputs, and where data were not found, EPA used air concentration data for other chemicals in comparable conditions of use or modeling estimates for some air concentrations. For other dermal exposure inputs, EPA used NMP weight fractions in formulations, durations of exposure, and exposed skin surface areas, body weight, and glove protection factors, if applicable. EPA used literature sources for estimating many of these occupational exposure parameters and generic assumptions when data were not available.

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.

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 cm^2 (mean for females),1070 cm^2 (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 cm^2 (females), 535 cm^2 (males)).

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.

Because of the expected use pattern for consumer products, EPA focused its assessment on acute exposures to consumers using various products that contain NMP. EPA used data from literature sources where available. In the absence of data, EPA relied on information regarding use patterns and physical-chemical properties of NMP for inputs used in the Consumer Exposure Module of the Exposure and Fate Assessment Screening Tool used to estimate acute exposure to consumers. EPA used two different approaches to quantify acute exposures. The first approach incorporated assumptions based on the duration of use; the second approach incorporated assumptions regarding consumer use on a single project (e.g., table, chest of drawers or bathtub).

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.

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.

4. Human Health Effects (Section 3.2 of the Draft Risk Evaluation):

EPA evaluated human health hazards as follows:

- Reviewed reasonably available human health hazard data and determined whether specific subgroups may have greater susceptibility to NMP hazard(s) than the general population.
- Conducted hazard identification (the qualitative process of identifying non-cancer and cancer endpoints) and dose-response assessment (the quantitative relationship between hazard and exposure) for all identified human health hazard endpoints.
- Derived points of departure (PODs) where appropriate; conducted benchmark dose

modeling depending on the available data. Adjusted the PODs as appropriate to conform to the specific exposure scenarios evaluated (e.g., adjust for duration of exposure).

- Considered the route(s) of exposure (oral, inhalation, dermal), available route-to-route extrapolation approaches, available biomonitoring data and the available approaches to correlate internal and external exposures to integrate the exposure and hazard assessments.
- Evaluated the weight of the scientific evidence based on the available human health hazard data for NMP.

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?

4.2 Please comment on the conclusions regarding the genotoxic and carcinogenic potential of NMP.

EPA considered two endpoints for the assessment of human health risks associated with chronic exposure to NMP, including a developmental toxicity endpoint (decreased fetal body weight) observed in numerous developmental toxicity studies, and a reproductive toxicity endpoint (decreased male and female fertility) observed in some reproductive toxicity studies. EPA considered the developmental endpoint of fetal mortality for assessment of human health risks associated with acute exposure to NMP.

4.3 Please comment on the validity of endpoints considered as the basis for PODs and their relevance to the evaluation of human health risks across lifestages.

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.

4.5 Please comment on the strength of evidence for, and the general applicability of decreased fetal body weight and decreased fertility for evaluating the human health risks associated with chronic exposure to NMP.

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.

5. Dose-Response Assessment (Section 3.2.5 of the Draft Risk Evaluation):

EPA used benchmark dose (BMD) modeling where practicable and, when BMD values were adequate, they were used to generate the POD for characterizing risks for chronic and acute exposure scenarios. EPA determined that use of developmental and reproductive endpoints for risk estimation would be protective of other sensitive subpopulations.

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 (C_{max}) and chronic (AUC) PODs.

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.

6. Risk Characterization (Section 4 of the Draft Risk Evaluation):

After consideration of all identified information, EPA concluded that NMP presents an unreasonable risk of injury to workers by inhalation and dermal exposure based on the potential for adverse human health effects (fetal mortality, decreased fertility, and decreased fetal bodyweight). EPA also concludes that NMP does not present an unreasonable risk of injury to occupational non-users by inhalation exposure (see Sections 4.2 and 5.1.2) or to environmental receptors exposed via surface water (see Section 4.1, supported by Appendix D). EPA makes this determination considering risk to potentially exposed and susceptible subpopulations identified as relevant, under the conditions of use without considering costs or other non-risk factors.

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).
6.2 Please comment on the validity of specific confidence summaries presented in sections 4.2 and 4.3.
6.3 Please comment on any other aspect of the human health risk characterization that has not been mentioned above.

EPA quantified non-cancer risks based on the Margin of Exposure (MOE), which is the Calculated by dividing the point of departure (POD) by scenario specific exposure estimates. EPA calculated MOEs for acute or chronic exposures separately based on the appropriate noncancer POD and estimated exposure concentrations adjusted for durations. To determine if unacceptable risks were present for relevant exposure scenarios, the endpoint-specific MOEs were compared to the benchmark MOEs. If the calculated MOE was less than the benchmark MOE, this indicated a human health risk.

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.

The peer-reviewed human PBPK models for NMP allow EPA to estimate total human exposures from combined inhalation and dermal exposures associated with specific exposure scenarios. The relative exposures from dermal, inhalation and vapor through skin can be deduced by comparing

the internal exposure to workers due to inhalation, vapor through skin and dermal liquid contact with internal exposure to ONUs due to inhalation and vapor through skin exposure (a subtraction technique).

6.5 Please comment on this approach to evaluating the relative contribution of each exposure route to aggregate risk.

The Frank R. Lautenberg Chemical Safety for the 21st Century Act (2016; amended TSCA (TSCA §§ 6b[4a]) requires that "potentially exposed or susceptible subpopulations" (PESS) be considered in the risk evaluation process.

6.6 Please comment on whether the risk evaluation has adequately addressed potentially exposed or susceptible subpopulations.

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.

EPA's characterization of the human health risks of NMP exposure are based on internal dose estimates of dermal and inhalation exposure. For workers, these estimates are calculated by multiplying the high end and central tendency MOE (without personal protective equipment) by the assigned glove protection factors (PFs) of 5, 10, or 20.

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.

7. Content and Organization:

EPA's Final Rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726) stipulates the process by which EPA is to complete risk evaluations under the Frank R. Lautenberg Chemical Safety for the 21st Century Act, To that end, EPA has completed a draft risk evaluation for NMP.

As part of this risk evaluation for NMP, EPA evaluated potential environmental and occupational exposures. The evaluation considered reasonably available information, including manufacture, use, and release information, and physical-chemical characteristics. It is important that the information presented in the risk evaluation and accompanying documents is clear and concise and describes the process in a scientifically credible manner.

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.

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.