

Comments of the
Semiconductor Industry Association (SIA)
On the
Draft Toxic Substances Control Act (TSCA) Risk Evaluation for
N-Methylpyrrolidone (NMP)

84 Fed. Reg. 60,087 (Nov. 7, 2019)

[EPA–HQ–OPPT–2019–0236; FRL–10001–87]

Submitted January 21, 2020

The Semiconductor Industry Association (SIA)¹ appreciates the opportunity to submit the following comments to the U.S. Environmental Protection Agency (EPA) on the Draft Toxic Substances Control Act (TSCA) Risk Evaluation for N-Methylpyrrolidone (NMP).

Executive Summary

Based on data submitted in these comments and previously submitted data, we respectfully ask that EPA consider the conditions of use in the semiconductor manufacturing sector, separately from those in other industrial activities and sectors. In this more focused evaluation, we request that EPA correct mistaken assumptions in its modeling on the conditions of use and worker exposure in the semiconductor manufacturing industry, and as a result its erroneous conclusion that the use of NMP in semiconductor manufacturing presents an “unreasonable risk” from dermal exposures to semiconductor workers. Specifically, EPA incorrectly assumed that semiconductor workers had dermal exposure to NMP over extended durations, and its models therefore overestimated the risks to health from these exposures.

SIA conducted an independent analysis, using EPA’s physiologically based pharmacokinetic (PBPK) model and relying on more accurate assumptions of workplace exposures under the conditions of use, and found that there is no unreasonable risk of injury to human health to workers from the conditions of use of NMP in the semiconductor manufacturing industry (hereafter referred to as “semiconductor industry”). If the conditions of use in the semiconductor industry are considered independently of the various broad categories (such as electronics parts manufacturing) with which EPA appears to have clustered semiconductor manufacturing, and the data SIA has provided are thoroughly considered in the proper context, then the weight of the evidence will demonstrate that the use of NMP does not present unreasonable risks to

¹ SIA is the trade association representing leading U.S. companies engaged in the design and manufacture of semiconductors. Semiconductors are the fundamental enabling technology of modern electronics that has transformed virtually all aspects of our economy, ranging from information technology, telecommunications, health care, transportation, energy, and national defense. The U.S. is the global leader in the semiconductor industry, and continued U.S. leadership in semiconductor technology is essential to America’s continued global economic leadership. More information about SIA and the semiconductor industry is available at www.semiconductors.org.

workers in the semiconductor industry. Accordingly, 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 the conditions of use in the sector require no further regulatory scrutiny under Section 6 of TSCA.

SIA's comments on the draft NMP Risk Evaluation focus solely on the Agency's preliminary finding of "unreasonable risk" from dermal exposures to workers. We concur with EPA's finding that the use of NMP in semiconductor manufacturing do not present an unreasonable risk of injury to the environment and therefore do not address those conclusions in these comments; however, SIA reserves the right to address environmental risk issues in a future filing if the EPA changes its preliminary determination in its final Risk Evaluation.

I. EPA INAPPROPRIATELY GROUPED SEMICONDUCTOR MANUFACTURING IN OTHER BROAD INDUSTRY CATEGORIES

EPA's draft Risk Evaluation improperly grouped semiconductor manufacturing along with other industrial activities which have differing conditions of use. For instance, semiconductor manufacturing was 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). 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. By 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. 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.

As documented by SIA in information provided to EPA (see footnotes 3 and 4), semiconductor manufacturing is considerably different from these other industrial operations and EPA was in error in grouping it with these other categories. Semiconductor manufacturing involves the fabrication of circuits that are typically less than 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 are, by design, intended to isolate the manufacturing process and chemicals from workers. Under these near-pristine and highly controlled conditions, there are no unreasonable risks to workers attributable to dermal exposures to NMP.

Notwithstanding this information which differentiates the conditions of use and exposure to NMP in semiconductor fab operations from other industrial processes, EPA incorrectly grouped uses of NMP in the semiconductor industry along with other industrial operations. As a result of this grouping, EPA incorrectly applied the same assumptions and drew the same conclusions that may be applicable to these other broader 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. When such information is readily available and the information has been determined by EPA reviewers to be of high quality (as was determined here), then it represents the best information for evaluating such conditions of use and consequently should be weighted heavily when applying a weight-of-the-evidence approach.

II. EPA MADE INCORRECT ASSUMPTIONS AND REACHED ERRONEOUS CONCLUSIONS

A. SIA Study Finds Flaws in EPA's Model and Conclusions

In finding that the use of NMP presented an “unreasonable risk” to workers under the conditions of use in the electronics manufacturing industry, EPA incorrectly grouped semiconductor manufacturing with other electronics manufacturing and made a number of invalid assumptions that led to this flawed conclusion. In order to better understand and validate EPA's findings, SIA requested and EPA subsequently provided the code for the PBPK model. SIA retained Cardno ChemRisk to review the EPA model and run the model using correct assumptions. The full report (“Cardno Report”) is attached at Attachment A.²

The Cardno report demonstrates that the EPA conclusions are mistaken based on incorrect assumptions. Among other things, the report concludes:

Our review of the U.S. EPA assumptions for semiconductor manufacturing found that the agency assumed prolonged liquid contact of one or two hands for 30 or 60 hours per week, respectively, under conditions equivalent to immersion in concentrated (generally >50% for most scenarios) or neat NMP. We concluded that this assumption did not represent a plausible central (e.g. median) or high-end (e.g. 95th percentile) condition of use for the semiconductor industry based on the description of the tasks that had been provided by SIA (2019a) to the U.S. EPA.

Using more accurate assumptions that reflect real-world practices in semiconductor manufacturing, the Cardno report states:

² “Review and Refinement of Semiconductor Manufacturing Occupational Exposure Scenarios: October 2019 U.S. EPA Draft Risk Evaluation for N-Methylpyrrolidone (NMP)” (January 17, 2020).

We found that refinement of the semiconductor manufacturing scenarios resulted in a conclusion that use of NMP in the semiconductor manufacturing industry does not present an unreasonable risk, which was supported by a review of the weight of evidence and an uncertainty analysis.

The report concludes: “The resultant acute and chronic MOEs were greater than 30 indicating support for a conclusion that use of NMP in the semiconductor manufacturing industry does not present an unreasonable risk.”

B. EPA Failed to Consider Properly Information Provided by SIA

In addition to these comments, over the past several years SIA has provided extensive additional information to EPA on the industry’s practices and procedures for handling NMP. Taken as a whole, these materials demonstrate that the highly complex processes involved in manufacturing advanced semiconductors, and the operational practices and engineering controls employed when handling chemicals at semiconductor fabs, effectively mitigate employee exposures to NMP at a fab. Among other things, SIA has submitted to EPA the following:

- Contemporary information on worker exposure at semiconductor fabs collected by member companies.³ These data included 118 air sampling datasets and details regarding the durations and frequencies of tasks undertaken by workers in fab facilities.
- SIA met with EPA officials in November 2017 to summarize the conditions of use of NMP at semiconductor fabs.
- SIA hosted a group of EPA officials in February 2019 to tour a semiconductor fab of a member company to provide a first-hand understanding of the use and handling of chemicals at a fab.

³ SIA N-Methylpyrrolidone Risk Management Measures and Worker Exposure Monitoring Results (February 22, 2019). This study was determined to be of high quality by EPA assessors. We also provided the Agency with data from monitoring at fabs in Europe, which we determined were accurate and representative of the exposure rates likely to be found at semiconductor fabs in the United States. SIA Comments To the EPA Docket on Methylene Chloride and N-Methylpyrrolidone (NMP) (EPA Docket # EPA-HQ-OPPT-2016-0743) (Submitted September 18, 2017). SIA incorporates by reference this submission into these comments.

- Several submissions to EPA⁴ describing 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, 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.⁵

This information clearly demonstrates that fab workers have minimal opportunities for direct exposures to NMP and use PPE and engineering controls that reduce exposures to levels which present no unreasonable risks to human health.

Unfortunately, it appears that much of the information and data 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 which should be corrected before the final Risk Evaluation is prepared and this must be 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.

C. Brief Summary of Errors in the Draft Risk Evaluation

In concluding that the use of NMP in semiconductor manufacturing posed an unreasonable risk of injury to worker health, EPA made several significant errors and relied on inaccurate assumptions. The Cardno report, included as Attachment A, uses the EPA PBPK model and highlights several of these errors. It concludes that, using

⁴ SIA submitted information to EPA at various stages in the NMP Risk Evaluation and rulemaking processes, including:

- a. SIA Comments On the Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: N-Methylpyrrolidone (NMP) (EPA-HQ-OPPT-2016-0743) (Submitted March 15, 2017).
- b. SIA Comments on EPA Proposal on Methylene Chloride and N-Methylpyrrolidone; Regulation of Certain Uses Under TSCA Section 6(a), 82 Fed. Reg. 7464 (Jan. 19, 2017) (EPA Docket # EPA-HQ-OPPT-2016-0231) (Submitted May 19, 2017).
- c. SIA Comments on Problem Formulation of the Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) CASRN: 872-50-4 (EPA-HQ-OPPT-2016-0743) (July 16, 2018).

SIA incorporates by reference each of these submissions into these comments.

⁵ Semiconductor manufacturing equipment – enclosed, interlocked, ventilated, and automated manufacturing equipment (tools) which separate employees from the product wafer and process chemicals. Contemporary tools are designed and fabricated to meet the requirements of SEMI S2 – *Environmental, Health, and Safety Guideline for Semiconductor Manufacturing Equipment* 11 and SEMI S6 – *Environmental, Health, and Safety Guideline for Exhaust Ventilation of Semiconductor Manufacturing Equipment*. The SEMI guidelines include provisions that ensure hazardous gases, fumes and vapors are controlled such that workplace concentrations are less than 1% of the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) or permissible exposure limit (PEL) during normal equipment operation. SEMI S2 requires emissions not exceed 25% of the TLV or PEL in the anticipated worst-case breathing zone during equipment failures and maintenance activities.

assumptions reflecting actual practices in the semiconductor industry, EPA should properly conclude that there is no risk from the use of NMP in the industry.

In finding that NMP posed a risk due to dermal exposure, EPA improperly determined that workers at semiconductor fabs would be in direct contact with NMP for prolonged periods of time. This assumption is in error. Workers in the semiconductor industry are trained extensively on the use of personal protective equipment (PPE) and companies have rigorous programs to ensure compliance with these requirements. In these comments SIA provides additional examples of the training of workers responsible for handling NMP and other chemicals. (Attachment B)

SIA submitted comments to the EPA Science Advisory Committee on Chemicals (SACC)⁶ that enumerate some of the more troublesome deficiencies of the draft Risk Evaluation. We summarize these points here and incorporate the SIA comments to the SACC (including the attachments) by reference:

- Only 5 of the 118 personal air samples that SIA member companies collected showed concentrations of NMP above the limits of detection. 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 that occur at many industrial sites and that are not specific to semiconductor manufacturing where measured exposures were <0.4 ppm and 1.2 ppm.
- Of the 5 measured samples that did have NMP concentrations above LOD, the highest 8 hr. 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 hr. TWA, more than a factor of 3 less than the 3.5 ppm ECHA limit and is 10 times lower than the AIHA's 10 ppm 8 hr. WEEL.
- SIA submitted details on the task durations and frequencies which showed task durations are short and human exposures are accordingly time-limited. EPA apparently did not use these data; instead, EPA's draft Risk Evaluation erroneously assumed workers could be exposed at such levels throughout their entire work shift (8-12 hours), rather than episodically.
- EPA Table 4-49 indicates that EPA made the assumption that semiconductor workers have direct dermal contact with liquid NMP and/or liquid mixtures of NMP. This assumption is entirely incorrect. SIA has described its engineering controls and chemical handling procedures to EPA in presentations and in written documentation that has been submitted to EPA (see Appendices A-C).

⁶ Comments of the Semiconductor Industry Association (SIA) To the Science Advisory Committee on Chemicals (SACC) On the Draft Toxic Substances Control Act (TSCA) Risk Evaluation for N-Methylpyrrolidone (NMP), 84 Fed. Reg. 60,087 (Nov. 7, 2019), [EPA-HQ-OPPT-2019-0236; FRL-10001-87], Submitted November 26, 2019. SIA incorporates by reference this submission into these comments.

These procedures are designed explicitly to prevent any dermal contact with liquid NMP or other potential forms of residual NMP.

- The Agency's application of a glove protection factor of 10 to the skin surface area because "workers ... are likely to wear gloves" and employees are likely to "have at least basic training on glove usage" is still mischaracterizing the industry's use of NMP. Skin surface area available for direct liquid dermal contact by fab workers should be considered zero for the purpose of this Risk Evaluation. The semiconductor industry uses specific procedures for selecting the proper gloves for the particular chemical and task. These procedures are documented, and cover both the selection of the glove, and the procedure for donning and removing the glove (see example training in the SACC comments at Appendix D). In recognition of these procedures, the glove protection factor should be at least, if not greater than, 20, and certainly not 10.
- SIA provided information on the extensive risk management measures and engineering controls employed in the semiconductor industry, including personal protective equipment (PPE). When modeling potential skin exposure, EPA did not reference the use of chemically resistant gloves such as the MAPA Trionic gloves⁷ (see SACC Comments at Appendix E) which are commonly used in the industry. Instead, the draft Risk Evaluation suggests EPA assumed that as much as one full hand or perhaps two hands are directly exposed. This is an incorrect assumption for this industry, is inconsistent with information SIA has provided to EPA, and does not reflect a weight-of-the-evidence approach.
- The basis for the Agency's handling of air sampling data with observations falling below detection limits is not transparent in the draft Risk Evaluation. Most of the data submitted by SIA reflected readings that were below detection limits and below the lowest US based occupational exposure limit, e.g., CAL OSHA PEL. The draft Risk Evaluation does not explain how non-detect data could lead to a preliminary conclusion that an 'unreasonable risk of injury to worker health' exists in semiconductor fab operations.
- NMP Concentrations in specific conditions of use should be considered. SIA provided data on NMP weight percentage in chemical formulations and waste as part of its 2019 study; this data should be used in the Agency's PBPK modeling and overall draft Risk Evaluation.

These are just some of the incorrect assumptions that served as the basis for EPA's erroneous conclusion. Using appropriate assumptions that accurately reflect practices in the semiconductor industry – as demonstrated by the Cardno report included in these comments – EPA should conclude that uses of NMP in semiconductor manufacturing does not present an unreasonable risk to workers.

⁷ Breakthrough time for N-methyl-2-Pyrrolidone 99% using MAPA Trionic gloves http://www.mapa-pro.com/our-gloves/protections/critical-environments/p/g/trionic-e-194.html#chemical_chart.

Conclusion

EPA incorrectly grouped semiconductor manufacturing with other industrial activities; moreover, the Agency relied on erroneous assumptions about the conditions of use of NMP in the semiconductor industry and the opportunity for and durations of dermal exposure. The weight of the evidence, when taking into account the considerable information SIA made available to EPA including the attached report from Cardno, does not support EPA's findings in the draft Risk Evaluation. SIA calls on EPA to recognize that the weight of the data and information reasonably available to EPA supports the conclusion that the conditions of use of NMP at semiconductor fabs do not present an unreasonable risk to the environment or to human health or worker safety. We call on EPA to meet its statutory and regulatory obligations concerning Risk Evaluations under Section 26 of TSCA and the implementing regulations at 40 CFR Part 702, by considering the conditions of NMP use in the semiconductor manufacturing sector independently from other industrial activities and sectors. To ensure it has performed a Risk Evaluation that is "well-tailored to the problems and decisions at hand" as required by 40 CFR 702.41(a)(5), EPA must carefully consider the workplace exposure data previously provided by SIA, and the information on employee training and workplace practices discussed by SIA and its members during the Peer Review meetings and in follow-up submissions. Applying the scientific standards established by the amendments to Section 26 of TSCA, the Agency must rely on these data because they constitute the "best available science" concerning the specific conditions of NMP use in the semiconductor industry.

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. Doing so will lead to Final Determination pursuant to 40 CFR §702.49(d) that the conditions of use of NMP in the semiconductor sector do not present an unreasonable risk to human health or the environment. Moreover, EPA should conclude the conditions of NMP use in the semiconductor sector require no further consideration for regulatory action under Section 6 of the Act.

Attachment A:
Review and Refinement of Semiconductor Manufacturing Occupational Exposure
Scenarios: October 2019 U.S. EPA Draft Risk Evaluation for N-Methylpyrrolidone
(NMP)
Cardno ChemRisk

Review and Refinement of Semiconductor Manufacturing Occupational Exposure Scenarios:

October 2019 U.S. EPA Draft Risk
Evaluation for N-Methylpyrrolidone (NMP)

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Appendices

Appendix A:	Updated U.S. EPA NMP PBPK Code
Appendix B:	IH SkinPerm Evaporation Analysis

Acronyms

AIHA	American Industrial Hygiene Association
AUC	Area under the curve
MOE	Margin of Exposure
NMP	N-Methylpyrrolidone
OEL	Occupational Exposure Limit
PBPK	Physiologically Based Pharmacokinetic
PF	Protection Factor
POD	Point of Departure
PVL	Liquid permeability constant
SIA	Semiconductor Industry Association
TSCA	Toxic Substances Control Act
TWA	Time-Weighted Average

Executive Summary

The U.S. EPA draft risk evaluation for N-Methylpyrrolidone (NMP) was released in November 2019 for public comment (U.S. EPA, 2019a). Cardno ChemRisk has been asked by the Semiconductor Industry Association (SIA) to review U.S. EPA's use of a physiologically based pharmacokinetic (PBPK) model to prepare the occupational exposure evaluation of semiconductor manufacturing workers. Our c included an evaluation of the U.S. EPA exposure assessment approach, as well as the preparation of a refined exposure assessment and risk characterization for semiconductor manufacturing workers based on a critical evaluation of the conditions of use in the industry. Our review included a consideration of the scientific standards of "best available science" and "weight of the scientific evidence" under the Toxic Substances Control Act (TSCA) as applied to the use of the PBPK model to determine internal worker exposures in the semiconductor industry. The benchmark dose-response modeling performed by U.S. EPA was not included in the scope of this review.

The U.S. EPA inappropriately grouped the conditions of use in the semiconductor manufacturing industry with other electronics manufacturing operations such as general electrical equipment or appliance manufacturing. The SIA (2019a, 2019b) has previously provided a detailed report and industrial hygiene information that describe the conditions of NMP use in semiconductor manufacturing. This data indicates that tasks involving the use of NMP are unlikely to be comparable to tasks performed in "electronic parts manufacturing" operations in other industrial sectors. Thus, the U.S. EPA should remove the assumption that "activities in the semiconductor manufacturing industry are representative of the operating conditions expected at other "electronic parts manufacturing" facilities, due to the use of similarly controlled operations" (U.S. EPA, 2019a, p. 100, l. 2067-2068). The remainder of this report addresses the conditions of use specific to the semiconductor manufacturing industry.

Cardno ChemRisk downloaded the U.S. EPA (2019b) PBPK model workspace file dated December 13, 2019, and verified the functionality of the model code for the "electronics part manufacturing scenario" using acslX Version 3.0.2.1. The functionality of the model was confirmed to be similar to the U.S. EPA version of the model as described in the main text and supplemental materials of Poet et al. (2016). We found that 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. The missing correction emphasizes the importance of U.S. EPA providing draft evaluation model set-up and code files when requested by interested stakeholders or peer reviewers. We also found that the model had not been adjusted to remove the female compartments (e.g. uterus or mammary tissue) for the male chronic exposure scenarios, but concluded that making these adjustments would have a negligible impact on the risk assessment conclusions. Cardno ChemRisk also found that the U.S. EPA stated an intention in the draft 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 (U.S. EPA, 2019a).

Our review determined that while many aspects of the 2019 U.S. 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, industry supplied or scientific consensus information. Our qualitative and quantitative sensitivity analysis showed that of the three pathways (inhalation, dermal vapor and dermal liquid), the only pathway contributing meaningfully to the U.S. EPA unreasonable risk determination for use of NMP in the semiconductor industry was dermal liquid contact. We found that the U.S. EPA screening analysis did not consider reasonably available information provided by the semiconductor industry concerning the potential for dermal liquid contact with NMP-containing liquid.

Our review of the U.S. EPA assumptions for semiconductor manufacturing found that the agency assumed prolonged liquid contact of one or two hands for 30 or 60 hours per week, respectively, under conditions equivalent to immersion in concentrated (generally >50% for most scenarios) or neat NMP. We

concluded that this assumption did not represent a plausible central tendency (e.g. median) or high-end (e.g. 95th percentile) condition of use for the semiconductor industry based on the description of the tasks that had been provided by SIA (2019a) to the U.S. EPA. We also found that prolonged exposure to concentrated or neat NMP is implausible (beyond worst case) because it is classified as a skin irritant potentially causing intolerable dermatitis, blistering or cracking of skin if exposure were to occur to the extent assumed in the draft evaluation. Finally, we found an implausible level of similarity in the U.S. EPA acute and chronic margins of exposure (MOEs) for semiconductor manufacturing scenarios with appreciably different tasks and opportunities for contact with NMP-containing liquid. This similarity was not consistent with the information provided by SIA to U.S. EPA, and presents an area requiring refinement and improvement for the evaluation to reflect the “best available science.”.

Cardno ChemRisk reviewed the semiconductor manufacturing risk management measures and industrial hygiene sampling data submitted by SIA (2019a, 2019b), and found the readily available information provided the industry comprehensive and sufficient for U.S. EPA to have assigned scenario-specific dermal liquid exposure factors that varied by scenarios. Furthermore, Cardno ChemRisk found that scientific consensus guidance documents were available to the U.S. EPA to facilitate the application of “best available science” to the PBPK internal exposure model scenario descriptions. For example, the current industrial hygiene dermal modeling tools and guidance available from the American Industrial Hygiene Association (AIHA) provide readily available means for refined dermal contact assessment when a screening level analysis (e.g. an assumption of prolonged immersion) suggests MOEs below the benchmark. As discussed in the AIHA guidance, solvent immersion scenarios with prolonged contact may not represent realistic occupational exposure scenarios.

The AIHA tools and guidance allow consideration of the amount of liquid deposited and the impact of evaporation time on dermal absorption potential. Cardno ChemRisk applied information from SIA, the estimates of evaporation time from the AIHA IH SkinPerm model, and the AIHA dermal exposure assessment guidance to prepare refined internal exposure estimates and MOEs for the semiconductor manufacturing scenarios. Estimates of loading, evaporation time and potentially exposed surface area were developed for each scenario.

An updated human PBPK analysis was performed using the U.S. EPA code in acslX Version 3.0.2.1. We made minor modifications to the U.S. model input template (an Excel file), .m file (an acslX script file), and the acslX .csl file (the model code file). The template was modified to input permeability constant, dermal contact time and days per week of exposure. The script file was modified to read these quantities from the input template, and define NMP density as a static parameter. The code file was modified to differentiate the dermal liquid contact time from the inhalation and dermal vapor exposure time. Dermal liquid contact was assumed to occur at the beginning of the shift for computational efficiency. We found that refinement of the semiconductor manufacturing scenarios to address incorrect U.S. EPA assumptions resulted in a conclusion that use of NMP in the semiconductor manufacturing industry does not present an unreasonable risk. Key assumptions of the refined analysis are presented in ES-1 and the chronic MOEs are presented in ES-2. As shown in ES-1, the updated analysis resulted in chronic MOEs greater than 30. A similar conclusion was reached for acute exposures.

Cardno ChemRisk considered the weight of evidence in support of the conclusion that use of NMP in the semiconductor industry does not present an unreasonable risk, and found that:

- Industrial hygiene information provided by SIA (2019a) indicated a low potential for exposure to NMP based well-described work and maintenance practices supported by air sampling data. This data indicated a low detection frequency of NMP with a suitably low detection limit (generally less than 1 ppm as compared NMP saturated vapor concentration of approximately 400 ppm at ambient temperature) to detect dispersive uses of the solvent or large surfaces with residual NMP. The low NMP concentrations at semiconductor facilities during routine or maintenance tasks are not indicative of the presence of liquid NMP, and therefore are inconsistent with EPA’s assumption of extensive dermal contact.

- Task descriptions provide by SIA (2019a) show that there are generally limited opportunities for skin contact with NMP-containing liquid based on the work descriptions. A limited number of maintenance tasks have a higher potential for dermal contact with residual NMP. However, operational conditions and engineering controls, such as flushing of NMP from filters prior to filter changes, limit the opportunity for contact with residual NMP. Additionally, in maintenance operations where there is a potential for contact with residual NMP, the technician wears PPE including gloves. The selection of PPE, donning, use and training is performed under specific procedures in the semiconductor industry,
- Strict work rules and procedures in the semiconductor industry indicate that the glove protection factor (PF) for specific activity training of 20 (95% efficiency) is appropriate,
- In contrast to the U.S. EPA draft evaluation where dermal liquid contact dominated internal exposure, Poet et al. (2016) describes the dermal liquid pathway as typically providing only “some contribution” to internal exposure, with inhalation identified as the primary route, and
- Consensus reviews of NMP (e.g. EC SCCS, 2011) note that prolonged skin contact with NMP can causes dermatitis, blistering or cracking of skin, thus indicating that the prolonged contact (one or two hands immersed in solvent for 30 or 60 hours per week, respectively) assumed in the U.S. EPA screening analysis is implausible.

In addition to the weight of evidence analysis, Cardno ChemRisk evaluated uncertainty in key determinants of internal exposure for the dermal liquid contact pathway including protection factor and permeability constants, and found that any potential uncertainty in these factors is not likely to impact the refined conclusion of safe use. Uncertainties in loading and surface area have been addressed in this analysis by selecting central tendency and high-end estimates. Uncertainty in potential acute (upset, or atypical) exposures not occurring on a chronic basis were assessed for a hypothetical plausible worst case event where 100% NMP was in contact with the palm side of two hands, with a resulting benchmark MOE > 30, indicating safe use. Uncertainty in the refined analysis was also addressed by the selection of precautionary exposure scenario parameters. For example, the maintenance scenarios assumed NMP contact during every shift, for the central tendency estimate, however, the opportunity for NMP contact at some facilities may appreciably less frequent.

In summary, our review found that the U.S. EPA's draft conclusion of unreasonable risk for the use of NMP in semiconductor manufacturing reflected a lack of refinement and the incorporation of incorrect assumptions in the screening scenario (one or two hands immersed in concentrated or neat NMP for 30 or 60 hours per week), rather than a reasonable characterization of the current conditions of use in the industry. Cardno ChemRisk reviewed the condition of use information provided by SIA (2019a), and developed refined exposure estimates for each semiconductor manufacturing scenario. This analysis indicates a differentiation of exposure potential between jobs, with some functions having no opportunity for direct dermal contact with NMP. The resulting acute and chronic MOEs were greater than 30, indicating support for a conclusion that use of NMP in the semiconductor industry does not present an unreasonable risk to workers.

Table ES-1: Explanation of PBPK input parameters [updates U.S. EPA (2019a) Table 2-33]

Work Activity	Scenario	Air Concentration Data	Shift Duration ^a	Exposure Frequency	Gloves	Skin Surface Area Exposed	Dermal Contact Time	NMP Weight Fraction
Container handling, small containers	Central Tendency	Central tendency (50 th percentile) of 12-hr TWA	12 hour shift	Once per shift, three shifts per week, 52 weeks per year	Yes, employees provided with comprehensive glove training	3 fingertips	With a dermal loading of 0.7 mg/cm ² , the evaporation time of NMP is approximately 20 minutes.	Central tendency (50 th percentile)
	High-end	High-end (95 th percentile) of 12-hr TWA		Once per shift, four shifts per week, 52 weeks per year		10 fingertips	With a dermal loading of 2.1 mg/cm ² , the evaporation time of NMP is approximately 60 minutes.	High-end (95 th percentile)
Container handling, drums	Central Tendency	Central tendency (50 th percentile) of 12-hr TWA	12 hour shift	Once per shift, three shifts per week, 52 weeks per year	Yes, employees provided with comprehensive glove training	3 fingertips	With a dermal loading of 0.7 mg/cm ² , the evaporation time of NMP is approximately 20 minutes.	Central tendency (50 th percentile)
	High-end	High-end (95 th percentile) of 12-hr TWA		Once per shift, four shifts per week, 52 weeks per year		10 fingertips	With a dermal loading of 2.1 mg/cm ² , the evaporation time of NMP is approximately 60 minutes.	High-end (95 th percentile)
Typical fab worker	Central Tendency	N/A	12 hour shift	Once per shift, three shifts per week, 52 weeks per year	Yes, employees provided with comprehensive glove training	No dermal exposure to NMP	No dermal exposure to NMP	Central tendency (50 th percentile)
	High-end	N/A		Once per shift, four shifts per week, 52 weeks per year		No dermal exposure to NMP	No dermal exposure to NMP	High-end (95 th percentile)
Fab worker w/ NMP container changeout	Central Tendency	"Photolithography formulations contain <5% NMP and may be NMP free" (SIA, 2019a); 50 th percentile of 0 and 5%	12 hour shift	Once per shift, three shifts per week, 52 weeks per year	Yes, employees provided with comprehensive glove training	No dermal exposure to NMP	With a dermal loading of 0.7 mg/cm ² , the evaporation time of NMP is approximately 20 minutes.	Central tendency (50 th percentile)
	High-end	"Photolithography formulations contain <5% NMP and may be NMP free" (SIA, 2019a); 95 th percentile of 0 and 5%		Once per shift, four shifts per week, 52 weeks per year		No dermal exposure to NMP	With a dermal loading of 2.1 mg/cm ² , the evaporation time of NMP is approximately 60 minutes.	High-end (95 th percentile)
Maintenance	Central Tendency	Central tendency (50 th percentile) of 12-hr TWA	12 hour shift	Once per shift, three shifts per week, 52 weeks per year	Yes, employees provided with comprehensive glove training	50% of the palm side of each hand	With a dermal loading of 0.7 mg/cm ² , the evaporation time of NMP is approximately 20 minutes.	Central tendency (50 th percentile)
	High-end	High-end (95 th percentile) of 12-hr TWA		Once per shift, four shifts per week, 52 weeks per year		70% of the palm side of each hand	With a dermal loading of 2.1 mg/cm ² , the evaporation time of NMP is approximately 60 minutes.	High-end (95 th percentile)

^a The typical duration fab operators and technicians perform work in the fab is 10.5 hours of a 12 hour shift (SIA, 2019a).

Table ES-1 (continued): Explanation of PBPK input parameters [updates U.S. EPA (2019a) Table 2-33]

Work Activity	Scenario	Air Concentration Data	Shift Duration ^a	Exposure Frequency	Gloves	Skin Surface Area Exposed	Dermal Contact Time	NMP Weight Fraction
Virgin NMP truck unloading	Central Tendency	Single value	8 hour shift	Once per year	Yes, employees provided with comprehensive glove training	10 fingertips	With a dermal loading of 0.7 mg/cm ² , the evaporation time of NMP is approximately 20 minutes.	Central tendency (50 th percentile)
	High-end	Single value	8 hour shift	Once per year		50% of the palm side of each hand	With a dermal loading of 2.1 mg/cm ² , the evaporation time of NMP is approximately 60 minutes.	High-end (95 th percentile)
Waste truck loading	Central Tendency	Single value	8 hour shift	Once per month	Yes, employees provided with comprehensive glove training	10 fingertips	With a dermal loading of 0.7 mg/cm ² , the evaporation time of NMP is approximately 20 minutes.	Central tendency (50 th percentile)
	High-end	Single value	8 hour shift	Once every three weeks		50% of the palm side of each hand	With a dermal loading of 2.1 mg/cm ² , the evaporation time of NMP is approximately 60 minutes.	High-end (95 th percentile)

^a The typical duration fab operators and technicians perform work in the fab is 10.5 hours of a 12 hour shift (SIA, 2019a).

Table ES-2: Non-cancer risk estimates for chronic exposure [updates U.S. EPA (2019a) Table 4-28]

Work Activity	Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Scenario	Weekly Average Chronic Exposure, AUC	Annual Frequency	Annual Average Chronic Exposure, AUC	Annual Average MOE	Benchmark MOE
				(hr mg/L)		(hr mg/L)		
Container handling, small containers	Reproductive Effects Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.09	50	0.09	2018	30
			High-end	0.22	50	0.21	864	30
Container handling, drums	Reproductive Effects Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.01	50	0.01	31345	30
			High-end	0.44	50	0.43	430	30
Typical fab worker	Reproductive Effects Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.02	50	0.02	7777	30
			High-end	0.10	50	0.09	1983	30
Fab worker w/ NMP container changeout	Reproductive Effects Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.02	50	0.02	7717	30
			High-end	0.10	50	0.10	1883	30
Maintenance	Reproductive Effects Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.05	50	0.04	4151	30
			High-end	0.64	50	0.61	298	30
Virgin NMP truck unloading	Reproductive Effects Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.20	1	0.004	48186	30
			High-end	0.27	1	0.01	34727	30
Waste truck loading	Reproductive Effects Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.04	12	0.01	22160	30
			High-end	0.11	17.3	0.04	5179	30

Note: Exxon, 1991 cited as "Exxon, B. (1991). Project No. 236535, 26 Nov 1991. ((sponsored by GAF Corp., Wayne, USA). (as 7044 cited in OECD, 2007)). Wayne, USA: GAF Corp." in U.S. EPA, 2019a.

1 Introduction

The U.S. EPA released a draft risk evaluation for N-Methylpyrrolidone (NMP) in November 2019 for public comment. Cardno ChemRisk has been asked by the Semiconductor Industry Association to review U.S. EPA's use of a physiologically based pharmacokinetic (PBPK) model to prepare the occupational exposure evaluation of semiconductor manufacturing workers. Our review includes an evaluation of the U.S. EPA approach, as well as the preparation of a refined exposure assessment and risk characterization for semiconductor workers based on a critical evaluation of the conditions of use in the industry.

TSCA Section 26 requires that risk assessments performed under the rule follow scientific standards, including "best available science" and "weight of the scientific evidence" (U.S. EPA, 2017; p. 33726). Section 26(h) provides factors relevant to models that should be considered, including the degree to which the method is "consistent with the intended use," has documented the "degree of clarity and completeness," has considered variability and uncertainty, and has been subject to an "independent verification or peer review of the information" (U.S. EPA, 2017; p. 33727). The U.S. EPA further clarified the TSCA requirements for models in the "Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act" rule published on July 20, 2017. The rule states that the agency will use "reasonably available information including information, models, and screening methodologies" as needed (U.S. EPA, 2017; p. 33751). The selection of methods will consider "the quality of the information, the deadlines specified in TSCA section 6(b)(4)(G) for completing the risk evaluation, and the extent to which the information reduces uncertainty" (U.S. EPA, 2017; p. 33751).

Under the rule, "best available science" is defined as "science that is reliable and unbiased" (U.S. EPA, 2017; p. 33731). The "weight of scientific evidence" is defined as "a systematic review method using "a pre-established protocol to comprehensively, objectively, transparently, and consistently, identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance" (U.S. EPA, 2017; p. 33733). The rule also states that best available science "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)" (U.S. EPA, 2017; p. 33748).

Our review of the U.S. EPA draft semiconductor manufacturing exposure scenarios has been conducted in consideration of the "best available science" and "reasonably available information" requirements of TSCA. Our review included a consideration of the scientific standards of "best available science" and "weight of the scientific evidence" under TSCA as applied to the use of the PBPK model to determine internal worker exposures in the semiconductor industry. The benchmark dose-response modeling performed by U.S. EPA was not included in the scope of this review

Included in this report are:

- A review of the U.S. EPA NMP PBPK model implementation including recommendations for increased transparency and use of peer-reviewed information (Section 2),
- The identification of sensitive exposure parameters for the semiconductor manufacturing scenario (Section 3),
- A critical evaluation of U.S. EPA exposure scenario assumptions for the semiconductor manufacturing scenario (Section 4),
- The preparation of refined exposure estimates and risk characterization for the semiconductor industry (Section 5),
- An uncertainty analysis (Section 6), and
- A conclusion of safe use of NMP in the semiconductor industry (Section 7).

2 Review of U.S. EPA NMP PBPK Model

Cardno ChemRisk downloaded the U.S. EPA Human NMP PBPK model files dated December 13, 2019 from the agency website (U.S. EPA, 2019b). The key electronic files relevant to the semiconductor manufacturing Scenario include:

- **HumPregRev2.clean.csl**: PBPK acslX model code
- **human_avg_params.m**: acslX script file containing U.S. EPA calibrated parameters including Michaelis -Menten kinetic constants, urinary first order elimination rate and dermal vapor permeability coefficient
- **human_params.m**: Additional model input parameters
- **NMP_wrkplc_2019_Sept04Femalev2.xls** and **NMP_wrkplc_2019_Sept04Malev2.xls**: Microsoft Excel file containing model input and output for acute female and chronic male worker exposure scenarios
 - **Cell A2**: Row number of last scenario in spreadsheet
 - **Cell B2**: Body weight (kg)
 - **Column H**: NMP weight fraction (unitless)
 - **Column I**: Exposed surface area (cm²)
 - **Column J**: Exposure duration (hours)
 - **Column L**: Duration based air concentration (mg/m³)
 - **Column O**: Glove protection factor (unitless)
 - **Column U**: Model estimated area under the curve for male chronic scenario (h-mg/L as a weekly average) assuming no decrease in vapor exposure due to mask
 - **Column V**: Model estimated peak serum concentration for female acute scenario (mg/L) assuming no decrease in vapor exposure due to mask
- **wrkplc_2019.m**: Script file loading human parameters and scenario assumptions as well as directing model execution and writing output to the Excel spreadsheet
 - Assign permeability constant of liquid
 - Assign exposure frequency
 - Assign model run duration
 - Assign fraction of skin exposure

Cardno ChemRisk evaluated the content of these files with a specific focus on the agency's evaluation of semiconductor manufacturing. Cardno ChemRisk verified that the model was similar to the model published by Poet et al. (2016), and identified a typographical error in the model code published with the 2016 paper based on an examination of the draft 2019 U.S. EPA model code (Section 2.1). Cardno ChemRisk also found the U.S. EPA approach to the dermal liquid contact pathway did not consider the comprehensive and readily available information provided by SIA, and no basis was provided to justify the assumption that prolonged contact (6 or 12 hours each work day) of NMP-containing liquid with skin is plausible (Section 2.2). Furthermore, the U.S. EPA assumptions about dermal liquid contact were not substantiated with peer reviewed literature. Additional concerns are addressed in Sections 2.3 through 2.5.

2.1 Verification of Model

An important consideration in the application of “best available science” to modeling evaluations under TSCA is the use to the extent possible of peer reviewed primary and supporting information. The U.S. EPA calibration of the NMP PBPK model used in the draft 2019 evaluation is described in the Poet et al. (2016) peer reviewed publication. Cardno ChemRisk imported the code from Poet et al. (2016) as well as the code used in the 2019 draft evaluation (U.S. EPA, 2019b) into acslX Version 3.0.2.1 to evaluate potential differences between the model used to assess semiconductor manufacturing scenarios and the model published in the peer review literature.

The model used in the 2019 draft evaluation appears to reflect the U.S. EPA “modified version” described in the 2016 peer-review publication. Cardno ChemRisk successfully reproduced the U.S. EPA peak and AUC presented in Table 5 of Poet et al. (2016) using the code in the draft evaluation production dated

December 13, 2019 (U.S. EPA, 2019b). We note, however, that the human code published in the 2016 peer-reviewed publication contained an error that appears to have been corrected by the U.S. EPA in the results presented in the publication, but not incorporated into the code presented in the supplemental materials of the manuscript. Thus, it would have been very difficult for an independent reviewer of the 2019 draft evaluation made public in November 2019 (U.S. EPA, 2019a) to reproduce the results presented by the agency using publicly available information until the agency released the code in mid-December 2019 (U.S. EPA, 2019b). This oversight emphasizes that public disclosure of the model code used in future draft evaluations is an important component of the transparency and “best available science” principles of TSCA.

Cardno ChemRisk found a typographical error in the publicly available Poet et al. (2016) supplemental material model code presented in section “A.5 Pregnant Human PBPK model code.” The publicly available code does not reflect a correction made by the U.S. EPA which became apparent to Cardno ChemRisk after reviewing the code posted on December 13, 2019 (Table 2.1). Specifically, the 2019 draft code used by U.S. EPA correctly defines a skin:blood partition coefficient, $pskb$, and applies this coefficient in the skin compartment. The publicly available code did not reflect that this correction had been made. The results presented in the 2016 peer reviewed publication appear to reflect the correct equations shown in Table 2.1.

Table 2-1: Comparison of 2016 public code to 2019 agency code human skin:blood partition coefficient

Element	Poet et al. (2016) Supplemental Materials	U.S. EPA Code dated December 13, 2019	Comment
1	Not defined	$PSKB=0.099$	PSKB is the skin:blood partition coefficient, and was not included in 2016 code
2	$CvSKL = CSKL/PSKL$	$CvSKL = CSKL/PSKB$	CvSKL is the concentration in venous blood exiting liquid exposed skin. The partition coefficient between blood and liquid (PSKL) is incorrectly presented in the 2016 supplemental materials
3	$CvSKv = CSKL/PSKL$	$CvSKv = CSKL/PSKB$	CvSKv is the concentration in venous blood exiting vapor exposed skin. The partition coefficient between blood and liquid (PSKL) is incorrectly presented in the 2016 supplemental materials

Cardno ChemRisk also notes that the density of NMP is not defined as static variable in the .m file of the 2019 U.S. EPA code. Thus, if the model is executed in a new acslX workspace, it is necessary to explicitly define density in the script file as shown in Attachment A.2.

In summary, the decision of the agency to release the NMP PBPK code used in the 2019 draft evaluation (U.S. EPA, 2019a) represented a prudent policy decision because the only publicly available information in the peer reviewed publication contained a typographical error impacting the ability of external reviewers to readily verify the agency’s assessment. The U.S. EPA PBPK guidance states, “PBPK models intended for risk assessment applications should be evaluated for quality and transparency” (U.S. EPA, 2006, p. 3-1) and that “adequate documentation is essential to the transparency and reproducibility of risk assessments” (U.S. EPA, 2006, p. 3-28). Thus, public release of the code reflects the important risk assessment principle of transparency and oversight through stakeholder peer review.

2.2 Identification of PBPK Model Estimates Lacking Sufficient Basis in Peer Reviewed Literature

Many aspects of the U.S. EPA 2019 NMP PBPK model are adequately supported by primary and secondary peer reviewed literature, particularly with respect to the inhalation and dermal vapor exposure routes. In contrast, the use of the model to assess dermal liquid exposures lacks reference to sufficient peer reviewed information, including a failure to consider:

- Reasonably anticipated relative contribution of inhalation, dermal vapor and dermal liquid contact to dose given the properties and hazard characteristics of NMP,
- Reasonably anticipated differences in dermal contact potential between industries and jobs, and

- Reasonably anticipated loading of liquid NMP on skin and duration of contact accounting for evaporation.

Thus, as described in more detail below the dermal liquid route estimates of AUC and peak serum concentration do not represent “best available science” as defined under TSCA.

2.2.1 Contribution by route

The reasonably anticipated contribution of each of the three routes of occupational exposure (inhalation, dermal vapor, and dermal liquid) to acute or chronic internal exposure is not adequately discussed in the 2019 draft evaluation (U.S. EPA, 2019a). A review of the expected contributions by route reflects an important step in model evaluation, and helps add weight to the plausibility of the model predictions. 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. Of importance is the observation that there are no scenarios where hands or other body parts are immersed in NMP-containing liquids. Based on the SIA work descriptions, certain maintenance tasks have a higher potential for dermal contact with residual NMP. However, operational conditions and engineering controls, such as flushing of NMP from filters prior to filter changes, limit the opportunity for contact with residual NMP. Additionally, in maintenance operations where there is a potential for contact with residual NMP, the technician wears PPE including gloves. The selection of PPE, donning, use and training is performed under specific procedures in the semiconductor industry. Thus, the fraction of exposure attributable to dermal liquid contact is likely to be negligible.

A review of Poet et al. (2016), and the 2019 draft evaluation (U.S. EPA, 2019a) indicates that U.S. EPA statements regarding the contribution of dermal liquid contact to exposure in the 2019 draft evaluation are inconsistent with statements made in the Poet et al. (2016) peer reviewed publication. Specifically, in Section A1.2 of the Poet et al. (2016) supplemental materials, the authors (including two authors affiliated with the U.S. EPA) write:

“Human exposures to NMP will be primarily via the inhalation route with some contribution from the dermal route (vapors or liquid).”

In contrast, Appendix I (line 1223 and 1224) of the 2019 draft evaluation (U.S. EPA, 2019a) states:

“Human exposures to NMP will be primarily via the inhalation route; contribution from the dermal route (vapors or liquid) may also be significant if not primary for some scenarios.”

The U.S. EPA has not provided a transparent substantiated analysis in the 2019 draft evaluation explaining the inconsistency in the stated contribution of liquid contact between the peer-reviewed paper and the draft TSCA evaluation. As shown in Section 3 below, the exposure assumptions adopted by the U.S. EPA for semiconductor workers imply that the dermal liquid contact contributes up to 99% of the chronic internal exposure, even with glove use assigned a protection factor (PF) of 20. This unexpectedly high contribution from dermal liquid contact reflects an assumption by the U.S. EPA that semiconductor workers are subject to an exposure scenario equivalent to the surface area of one or two hands immersed in NMP-containing liquid for 6 or 12 hours per shift (respectively), 5 days per week for 52 weeks per year. This assumption is inconsistent with information on conditions of use that the SIA provided to the agency (SIA, 2019a), as well as the intrinsic skin irritation hazard of NMP.

The limited contribution of occupational direct dermal contact to NMP internal exposure noted in Poet et al. (2016) reflects the hazard characteristics of the solvent. As noted at lines 3928-3929 in Section 3 of the draft evaluation, “[w]orkers exposed to NMP dermally experienced skin irritation.” More specifically, the E.U. Scientific Committee on Consumer Safety notes that “prolonged or repeated exposure” is associated with dermatitis, edema, redness, blister or cracking (E.U. SCCS, 2011). The semiconductor worker scenarios are characterized by 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 appears to be 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)

2.2.2 Differences in dermal contact potential

The current U.S. EPA assessment of dermal liquid contact in the semiconductor manufacturing sector reflects risk assessment policy decisions lacking consideration of “best available science.” Specifically, U.S. EPA’s dermal contact assumptions reference historical agency policy (e.g., the 1991 U.S. EPA Chemical Engineering Branch Manual) resulting in implausibly equivalent exposure scenario assumptions across heterogeneous industry sectors. For example, the U.S. EPA (2019a) assumed that one full hand (central tendency) or two full hands (high end) were in contact with NMP for all scenarios in the 2019 draft evaluation except “writing”. As noted above, this approach is equivalent to assuming immersion of one or two hands in NMP solvent for prolonged periods, which is implausible due to conditions of dermatitis, blistering or cracking that would be difficult to tolerate for prolonged periods of time. Further, it is implausible that the 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 and adhesives and semiconductor manufacturing.

The U.S. EPA assessment also fails to consider differences in training by assuming that no industry provides adequate specific activity training on glove use, removal and disposal. Across all industrial scenarios, the U.S. EPA assumes at most “basic” training is implemented resulting in a 90% glove efficiency, or PF of 10. In contrast, the ECETOC TRA v3 approach cited by the U.S. EPA recommends a PF of 20 (95% efficiency) with specific activity training. It is implausible that no industry with NMP uses provides the training and oversight necessary for proper glove use, removal and disposal. Such training is reasonably expected to be in place in most industries with sufficient potential for NMP contact with the skin due the skin irritation hazard of NMP.

2.2.3 Liquid dermal loading and contact time

The current dermal liquid contact exposure assumptions are based primarily on a policy rather than a “best available science” approach that considered detailed information supplied by the assessed industry. The equations used by the U.S. 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 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).

At least one peer-reviewed approach capable of using the scenario specific factors mentioned above 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). Importantly, this model allows for consideration of realistic exposure scenario factors including skin surface loading (mg/cm²) and contact time (h) based on a consideration of evaporation. As noted at the AIHA website, IH SkinPerm is a consensus product of the AIHA Exposure Assessment Strategies Committee, which recommends the Sahmel et al. (2009) chapter mentioned above as a “useful reference for understanding the science and terminology associated with skin permeation.”

In summary, the U.S. EPA approach to dermal liquid contact is not consistent with “best available science.” Prolonged contact of the skin surface area of one or two hands with NMP is implausible due to skin irritation hazards, and the reasonable assumption of adequate glove training programs was not considered. As discussed in more detail below, 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. Thus, the U.S. EPA unreasonable risk determination for the semiconductor manufacturing industry is unreliable. Refinements to the U.S. EPA PBPK model for semiconductor manufacturing are described in Sections 4 and 5 below.

2.3 Physiological Representation of the Male

Cardno ChemRisk notes that the female physiological compartments for the female were not removed for the male model runs NMP PBPK model referenced in the 2019 draft evaluation (U.S. EPA, 2019a). Cardno ChemRisk found that removing these compartments and reallocating the volume to slowly perfused tissue had a negligible impact on the model predictions. It is recommended that the U.S. EPA correct the physiological inputs for males and formally confirm this conclusion in their final evaluation.

2.4 Scope of Industries Addressed in Draft U.S. EPA PBPK Analysis

The U.S. EPA inappropriately grouped the conditions of use in the semiconductor manufacturing industry with other electronics manufacturing operations such as general electrical equipment or appliance manufacturing. The SIA (2019a, 2019b) provided a detailed description of the conditions of NMP use in semiconductor manufacturing, which indicates that tasks involving the use of NMP are unlikely to be comparable to tasks performed in “electronic parts manufacturing” operations in other industrial sectors. Thus, the U.S. EPA should eliminate the assumption that “activities in the semiconductor manufacturing industry are representative of the operating conditions expected at other “electronic parts manufacturing” facilities, due to the use of similarly controlled operations” (U.S. EPA, 2019a, p. 100, I. 2067-2068). In the revised risk evaluation, it is concluded that the standard of “best available science” can only be met if the semiconductor industry is assessed separately, rather than as part of a more broad “electronics parts manufacturing” sector. This report addresses the conditions of use specific to the semiconductor manufacturing industry.

3 Sensitivity Analysis

The draft U.S. EPA unreasonable risk determination for semiconductor manufacturing states that “[f]or all workers, the worker unreasonable risk determination reflects the severity of the effects associated with chronic exposures, even in the presence of expected PPE” (U.S. EPA, 2019a, p. 317). Additionally, it is stated that “[r]elevant factors that may generate uncertainties and affect the risk calculations include representativeness and age of the data for the condition of use, as well as “assumptions about glove use, glove effectiveness, duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP” (U.S. EPA, 2019a, p. 317). Notably, however, the U.S. EPA has not performed a sensitivity analysis to assess which of these factors contributed appreciably to estimation of MOEs less than the stated benchmark of 30.

3.1 Qualitative Sensitivity Analysis

Qualitatively, it is readily apparent that the inhalation and dermal vapor pathways contribute negligibly to internal exposure, and thus are not important contributors to the unsubstantiated U.S. EPA conclusion that semiconductor manufacturing MOEs are less than the chronic benchmark of 30 for container handling, drum handling, fab worker, maintenance, truck unloading and waste truck unloading.

The Poet et al. (2016) proposed chronic occupational exposure limit (OEL) considering inhalation and dermal vapor exposure is 24 ppm (97.2 mg/m³ assuming 4.05 mg/m³ per ppm at NTP). The high-end 12-hour time weighted averages (TWAs) presented in draft Table 2-66 are 0.608, 1.54, 0.405, 0.690 mg/m³ for small container handling, drum handling, fab worker and maintenance. Similarly, 8-hour TWAs are 4.78 and 0.709 mg/m³ for virgin NMP and waste NMP bulk loading, respectively. Each of the high-end airborne exposure concentrations assumed by the EPA for semiconductor manufacturing is more than an order of magnitude less than the OEL proposed by Poet et al. (2016). This conclusion is maintained even if the 12-hour TWA are increased to account for the 8-h TWA basis of the OEL proposed by Poet et al. (2016).

The U.S. EPA 2019 drafts proposes a somewhat more precautionary point of departure (470 h-mg/L with an uncertainty factor of 21 in Poet et al. (2016) as compared to 183 h-mg/L with a benchmark MOE of 30). Poet et al. (2016) demonstrate that an inhalation-only exposure of 460 ppm corresponds to an AUC of 470 h-mg/L using the U.S. EPA version of the model. Thus, an AUC of 183 h-mg/L approximately corresponds to a work-shift airborne exposure (i.e. excluding dermal vapor and dermal liquid routes) of 179 ppm or 725 mg/m³ (460 ppm x 183 h-mg/L / 470 h-mg/L). For example, it can be roughly approximated that the inhalation component of the fab worker will result in an MOE appreciably greater than 30, i.e. $725 \text{ mg/m}^3 / 0.405 \text{ mg/m}^3 \approx 1800$. The dermal vapor component is a small fraction of the inhalation component, representing about 19% of inhalation+dermal vapor internal exposure in the U.S. EPA model presented by Poet et al. (2016). Thus, the MOE for dermal vapor exposure only would be appreciably greater than 1800.

It is clear based on the order-of-magnitude qualitative assessment above that the U.S. EPA draft determination of unreasonable risk reflects the assumption of pervasive and persistent immersive skin contact with liquid NMP because the dermal vapor and inhalation routes alone result in MOEs appreciably greater than 30. Notably, the chronic MOEs for the semiconductor manufacturing scenarios was estimated to vary over the implausibly narrow range of 4 to 7. Such a narrow range is implausible due to wide variation in tasks performed in the semiconductor manufacturing scenarios, with reasonably anticipated variation in liquid dermal contact potential. It can be concluded based on the qualitative sensitivity analysis that the U.S. EPA should correct the skin contact with NMP-containing liquid assumptions used in the draft evaluation of the semiconductor manufacturing scenarios. In contrast, the risk assessment conclusions do not appear to be sensitive to assumptions regarding inhalation concentrations and dermal vapor exposure, and thus are a lower priority for refinement.

3.2 Quantitative Sensitivity Analysis

Cardno ChemRisk loaded the U.S. EPA workspace files with posting date of December 13, 2019 into acslX Version 3.0.2.1. A brief quantitative sensitivity analysis was performed for the fab worker to confirm the findings of the qualitative sensitivity analysis. This analysis included evaluating the percent contribution of each pathway to internal exposure, as well as a local sensitivity estimate assessing the percent change in internal exposure corresponding to a 10% change in surface area in potential contact with liquid NMP.

The U.S. EPA assumptions for the fab worker scenario are presented in Table 3-1, and the approximate percent contribution by route is presented in Table 3-2. The MOEs for inhalation-only were approximately 1900 to 5400, dermal vapor-only 10000 to 30000 and dermal liquid-only 0.3 to 240. Dermal liquid contact accounted for 95% to nearly 100% of the internal chronic exposure in the fab worker scenario. The high-end inhalation-only MOE of approximately 1860 was similar to the approximate estimate (1800) derived in the qualitative analysis.

Table 3-1: U.S. EPA fab worker scenario assumptions

Scenario	Glove PF	Dermal Contact Area (cm ²)	Dermal Contact Time (hours)	Inhalation TWA (mg/m ³)	Inhalation Time TWA (hours)	NMP Weight Fraction
EPA-Central tendency Fab worker	1	535	6	0.276	6	0.15
	10	535	6	0.276	6	0.15
	20	535	6	0.276	6	0.15
EPA-High End Fab worker	1	1070	12	0.405	12	0.999
	10	1070	12	0.405	12	0.999
	20	1070	12	0.405	12	0.999

Table 3-2: Approximate contribution by route for U.S. EPA draft Fab worker evaluation

Scenario	Glove PF	AUC by Route (hr-mg/L)				% of Total AUC			MOE			
		Dermal Liquid Only	Dermal Vapor Only	Inhalation Only	Total	Dermal Liquid Only	Dermal Vapor Only	Inhalation Only	Dermal Liquid Only	Dermal Vapor Only	Inhalation Only	Total
EPA-Central tendency	1	16	0.01	0.03	16	100%	0.04%	0.22%	12	26584	5453	12
	10	1.5	0.01	0.03	1.6	97%	0.40%	2.14%	120	29048	5447	117
	20	0.8	0.01	0.03	0.8	95%	0.77%	4.20%	240	29579	5447	228
EPA-High End	1	670	0.02	0.10	670	100%	0.003%	0.01%	0.3	9894	1858	0.3
	10	43	0.02	0.10	43	100%	0.04%	0.23%	4.3	9896	1856	4.3
	20	21	0.02	0.10	21	99%	0.08%	0.47%	8.8	10422	1856	8.7

A finding of appreciable sensitivity of the MOE to the inclusion or exclusion of the dermal liquid route is inconsistent with an expectation of “some contribution” of the route to total dose stated in the Poet et al. (2016) supplemental materials. Furthermore, such a conclusion is inconsistent with the description of the Fab worker provided to U.S. EPA in SIA (2019a), which indicates that that chemicals are not handled under routine conditions because the processes are automated and closed. Finally, appreciable dermal liquid contributions to internal exposure are implausible when NMP airborne concentrations are relatively low (relative to the Poet et al. (2016) proposed OEL), and in many cases in the SIA (2019a) dataset, below detection limits. The low, measured airborne concentrations (i.e. generally less than 1 ppm as compared NMP saturated vapor concentration of approximately 400 ppm at ambient temperature) suggest that dispersive releases of NMP are not occurring, limiting the opportunity for contact of liquid NMP with the skin.

A brief local sensitivity analysis was performed to evaluate the sensitivity of AUC to changes in the assumed dermal contact area with NMP-containing liquid. As expected, a 10% change in surface area resulted in an approximate 10% change in AUC. It can be concluded that the surface area and dermal contact time are highly sensitive parameters in the estimation of AUC, peak serum concentration and the acute and chronic semiconductor manufacturing scenarios.

4 Evaluation and Refinement of Draft U.S. EPA Semiconductor Manufacturing Scenarios

Cardno ChemRisk reviewed the semiconductor manufacturing risk management measures and industrial hygiene data submitted by SIA (2019a), and found the information provided sufficient for U.S. EPA to have assigned scenario-specific dermal liquid exposure factors that varied by scenarios. Airborne NMP was not detected in the majority of tasks sampled with most detection limits at a level of 1 ppm or lower. Thus, the sampling confirms that dispersive release of NMP is unlikely to occur in this industry, and the conditions of use including the use of closed processes and well-defined maintenance procedures limit NMP contact opportunities. In this section, each of the semiconductor exposure scenarios are briefly summarized with an explanation of the rationale for refinements or corrections of the scenario. The refinements and corrections primarily address the dermal liquid contact pathway, which was identified as the sensitive pathway for MOE determinations.

4.1 Glove Protection Factor

The U.S. EPA assumed that the maximum achievable glove PF was 10 (90% efficiency) stating that the “EPA has not found information that would indicate specific activity training (e.g., procedure for glove removal and disposal) for tasks where dermal exposure can be expected to occur in a majority of sites in industrial only OESs... (U.S. EPA, 2019a, p. 69, l. 1227-1230). As explained in the draft evaluation, a PF of 10 corresponds to “basic” training whereas a PF of 20 corresponds to additional training being provided. The semiconductor manufacturing tasks described in SIA (2019a) are performed under strictly controlled work rules. Thus, it is reasonable to assume glove use with a PF of 20 is appropriate for this industry. The sensitivity of the refined analysis to the assumption of specific activity training is evaluated in the uncertainty section of the report. Additional information on glove use and training has been provided in SIA (2019b).

4.2 Dermal Loading

The U.S. 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 to 2.1 mg/cm² for incidental contact with liquids (Sahmel et al. 2009). These estimates are based on prior U.S. EPA research, which found a mean amount of liquid retained on the surface of hands after subjects wiped their hands with a cloth saturated with cooking oil (Cinalli et al., 1992). For example, in the U.S. EPA study, 2.07 mg/cm² was retained after application and 0.75 mg/cm² was retained after partial removal of cooking oil with a dry cloth. As described in more detail by scenario below, 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 to 2.1 mg/cm².

4.3 Surface Area of Liquid Contact

The U.S. EPA assumed a surface area of liquid contact that is consistent with the AIHA recommendation in the absence of more detailed information. Sahmel et al. (2009) suggests a default surface area equal to the surface area of one to two hands for incidental contact with liquids. A review of the tasks described by SIA (2019a), however, indicates a much lower potential for liquid contact than the surface area of one to two hands. Thus, refined estimates of surface area are provided on a scenario-specific basis below. Refined surface areas can be derived from the U.S. EPA (2011) Exposures Factor Handbook. Table 4-1 presents the original EPA assumption along with reduced surface areas more representative of the dermal contact potential in the semiconductor industry.

Table 4-1: Refinement of surface area of skin exposed to NMP-containing liquid

Quantity	Surface area (cm ²)		Basis
	Male	Female	
U.S. EPA Exposure Factors Handbook			
Total hand (2 hands)	1070	890	U.S. EPA Exposure Factors Handbook, 2011
EPA Draft Risk Evaluation			
EPA NMP Central tendency	535	445	One hand - total SA
EPA NMP Upper Bound	1070	890	Two hands - total SA
Proposed Refinement			
Palmar total (2 hands)	535	445	Palms are 50% of total hands SA
50% of palms (2 hands)	267.5	222.5	
70% of palms (2 hands)	374.5	311.5	
Palmar fingertip (single tip)	8	7	Palmar surface area of one finger is 10% of palmar SA of one hand; one fingertip is 30% of palmar finger SA.
Palmar fingertip (3 tips)	24	20	
Palmar fingertip (10 tips)	80	67	

4.4 Contact Time

Many of the 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. Cardno ChemRisk determined reasonable contact time times for NMP based on the time estimated by IH SkinPerm (Tibaldi et al, 2014) for complete evaporation for loading of liquid NMP at a level of 0.7 or 2.1 mg/cm². The assumptions and results for the IH SkinPerm model are presented in Attachment B. The model indicated a time to complete evaporation of 20 and 60 minutes when the loading was 0.7 or 2.1 mg/cm², respectively. This conclusion was insensitive to surface area over the range of 10 to 1000 cm². Cardno ChemRisk confirmed that the dermal permeability constant used by the U.S. EPA of 4.78×10^{-4} was similar to the value of 3.66×10^{-4} predicted by the algorithm of IH SkinPerm, thus predictions of dermal absorption were similar in both methods.

A dermal liquid contact time of 20 minutes (central tendency) or 60 minutes (high-end) was assumed based on the IH SkinPerm model. Dermal liquid contact was assumed to occur at the beginning of the shift for computational simplicity.

4.5 Shift Duration and Weekly Frequency

The U.S. EPA assumed shift durations of 6 and 12 hours for 5 days per week (30 hours/week central tendency and 60 hours/week high-end). Cardno ChemRisk assumed a standard shift duration of 12 hours, during which fab operators and technicians typically perform work in the fabs for 10.5 hours as presented in SIA (2019a). The days per week of work was assumed to be 3 days per week (36 hours total shift time per week; central tendency) and 4 day per week (48 hours total shift time per week) for all scenarios except bulk virgin NMP and waste NMP handling where a shift time of 8 hours was assumed based on the sampling duration.

4.6 Personal Exposure Concentrations

The TWA air concentrations used in the refined model were based on the 12-hour TWAs presented in SIA (2019a) with the exception of bulk virgin NMP and waste NMP handling, which had only an 8-hour TWA available.

4.7 Liquid Permeability Constant

The U.S. EPA (2019a) selected dermal liquid permeability coefficients based on their modeling of a study where 12 volunteers (6 male and 6 female) were exposed to 300 mg NMP of either neat or diluted 50:50 in an aqueous solution. The derived values were similar (within a factor of approximately 2) to the values presented in Poet et al. (2016) peer-reviewed publication.

The draft evaluation states:

“...distinct values of the liquid permeability constant (PVL), 2.05×10^{-3} cm/h and 4.78×10^{-4} cm/h, were identified from the experimental data. The appropriate value of PVL for neat vs. diluted NMP was used in the respective exposure scenarios in this assessment” (U.S. EPA, 2019a, p. 200, l. 4758-4760).

Cardno ChemRisk notes that in the results presented in the draft U.S. EPA evaluation, a PVL of 4.78×10^{-4} cm/h appears to have been applied to all scenarios, irrespective of the weight percentage in the scenario. Thus U.S. EPA PBPK model used a PVL of 4.78×10^{-4} cm/h even in scenarios with neat NMP.

Similarly, Cardno ChemRisk selected a PVL of 4.78×10^{-4} cm/h for all semiconductor manufacturing scenarios including ones with weight percentages approaching 100% because prolonged contact with neat NMP is not expected occur in the industry. Prolonged contact with solvents can denature the cellular structure of the skin, and as a result, cause apparent permeability increases to a value greater than predicted by theoretical considerations. The potential impact of assuming the higher PVL for high-end scenarios where neat NMP is present is discussed in Section 6.2.3.

4.8 Fraction of skin exposed to dermal vapor

The U.S. EPA assumed that up to 25% of the skin is subject to dermal vapor exposure. The sensitivity analysis performed in this report indicated that inhalation and dermal vapor exposures were not important pathways with respect to the conclusions of the risk assessment. It is recommended, however, that the U.S. EPA acknowledge the conservatism of their analysis as some of the semiconductor manufacturing scenarios such as the fab workers are characterized by extensive garment coverage. For example, a fab worker's cleanroom suit, hood and boots were estimated to cover $\geq 98\%$ of the skin.

4.9 Exposure Scenarios

4.9.1 Container handling, small containers

The U.S. EPA assumed a scenario equivalent to one or two hands of immersion in NMP-containing liquid for a 6 hour or a 12 hour shift (30 to 60 hours per week) for 52 weeks per year for the small container handling scenario. Cardno ChemRisk notes that the task described in SIA (2019a) represents a very low potential for dermal contact, primarily limited to incidental contact with residual associated with the automated chemical delivery system during the container change. NMP was not detected in personal air sampling, suggesting low potential for residual NMP-containing liquid to contact skin. Notably, the presence of ventilation would enhance the evaporation of any residue thus limiting the potential for liquid NMP contact with the skin. The frequency of container changeout varies from once per week to once per six weeks per track tool, with variation in the number of tools between facilities. This refined analysis assumes container handling occurs each shift to account for variation in the number of tools, but it should be noted that at some facilities container changes do not occur daily.

The following revisions were made to the container handling scenario:

- Surface area potentially exposed to NMP-containing liquid: three (central tendency) to ten (high end) fingertips based on limited potential of contact with liquids containing NMP during container handling and changeout (see Table 4-1 for areas)
- Daily dermal loading: 0.7 mg/m^2 (central tendency) and $2.1 \text{ (high-end) mg/cm}^2$ (see Section 4.2)
- Daily dermal contact time: 20 minutes (central tendency) and 60 minutes (high end)
- Weekly shift frequency: 3 days per week, 12 hours per day (central tendency, 36 hours/week) or 4 days per week, 12 hours per day (high end, 48 hours per week) (see Section 4.5)
- Annual frequency: 50 weeks per year
- Glove use: Yes, PF=20 (95%) based on training programs and strict work rules

The refined scenario is considered to be conservative (likely to overestimate exposure) because most container changeout events are expected to result in a low potential for dermal contact based on the low detection frequency of NMP in sampled air. Additionally, the assumed contact time of 20 to 60 minutes

conservatively exceeds likely task times, which may be as low as 5 to 10 minutes. It is possible, although not likely, that non-routine events could occur resulting in an acute exposure potential somewhat greater than three to ten fingerprints possibly up to a surface area equal to the palm side of both hands. Acute exposures up to the palm side of both hands are evaluated in Section 6.4.2 of this report.

4.9.2 Container handling, drums

The U.S. EPA assumed a scenario equivalent to one or two hands of immersion in NMP-containing liquid for a 6 hour or a 12 hour shift (30 to 60 hours per week) for 52 weeks per year. Cardno ChemRisk notes that the task described in SIA (2019a) represents a very low potential for dermal contact, primarily limited to incidental contact with residual associated with dip tubes during the container change. NMP was not detected in personal air sampling, indicating low potential for residual NMP-containing liquid to contact skin. Notably, the presence of local exhaust ventilation would enhance the evaporation of any residue thus limiting the potential for liquid NMP contact with the skin. Leak detection and exhaust alarms further limit the potential for release. Most container changeout events are expected to result in *de minimis* dermal contact. The frequency of drum changeout varies from once per week to multiple times per shift. This refined analysis assumes container handling occurs each shift to account for variation between facilities, but it should be noted that at some facilities container changes do not occur daily.

The following revisions were made to the drum handling scenario:

- Surface area potentially exposed to NMP-containing liquid: three (central tendency) to ten (high end) fingertips based on limited availability of liquids containing NMP during drum handling and changeout (see Table 4-1 for areas)
- Daily dermal loading: 0.7 mg/m² (central tendency) and 2.1 (high-end) mg/cm² (see Section 4.2)
- Daily dermal contact time: 20 minutes (central tendency) and 60 minutes (high end)
- Weekly shift frequency: 3 days per week, 12 hours per day (central tendency, 36 hours/week) or 4 days per week, 12 hours per day (high end, 48 hours per week) (see Section 4.5)
- Annual frequency: 50 weeks per year
- Glove use: Yes, when potential for contact with NMP-containing liquid exists, PF=20 (95%) based on training programs and strict work rules

The refined scenario is considered to be conservative (likely to overestimate exposure) because most container changeout events are expected to result in *de minimis* dermal contact supported by the absence of detectable NMP in air. It is possible, although not likely, that non-routine events could occur resulting in an acute exposure potential somewhat greater than three to ten fingerprints possibly up to a surface area equal to the palm side of both hands. Acute exposures up to the palm side of both hands are evaluated in Section 6.4.2 of this report.

4.9.3 Typical fab worker

The U.S. EPA assumed a scenario equivalent to one or two hands of immersion in NMP-containing liquid for a 6 hour or a 12 hour shift (30 to 60 hours per week) for 52 weeks for year. Cardno ChemRisk notes that most fab workers do not contact NMP as described in SIA (2019a). It was noted however, that at some facilities, photolithography track operators change out small containers of NMP-containing photoresist. Thus, Cardno ChemRisk separately characterizes fab workers potentially performing container changes in Section 4.8.4 below.

The following revisions were made to uniquely characterize a typical fab worker:

- Surface area potentially exposed to NMP-containing liquid: none
- Weekly shift frequency: 3 days per week, 12 hours per day (central tendency, 36 hours/week) or 4 days per week, 12 hours per day (high end, 48 hours per week) (see Section 4.5)
- Annual frequency: 50 weeks per year

- Glove use: Yes, when potential for contact with NMP-containing liquid exists, PF=20 (95%) based on training programs and strict work rules

The refined scenario is considered to be conservative (likely to overestimate exposure) because most container changeout events are expected to result in *de minimis* dermal contact supported by the absence of detectable NMP in air. It is possible, although not likely, that non-routine events could occur resulting in an acute exposure potential somewhat greater than three to ten fingerprints possibly up to a surface area equal to the palm side of both hands. Acute exposures up to the palm side of both hands are evaluated in Section 6.4.2 of this report.

4.9.4 Fab worker w/ NMP Container Changeout

Some photolithography operators may change out small containers of photoresist or other formulations which contain NMP (SIA, 2019a). The parameters of the container handling scenario were applied to characterize fab workers with these responsibilities.

The following revisions were made characterize fab workers performing NMP container changeout:

- NMP weight percent of 2.5% (central tendency) and 5% (high-end) based on photolithography formulations containing up to <5% NMP (SIA, 2019a)
- Surface area potentially exposed to NMP-containing liquid: three (central tendency) to ten (high end) fingertips based on limited availability of liquids containing NMP during container handling and changeout (see Table 4-1 for areas)
- Daily dermal loading: 0.7 mg/m² (central tendency) and 2.1 (high-end) mg/cm² (see Section 4.2)
- Daily dermal contact time: 20 minutes (central tendency) and 60 minutes (high end)
- Weekly shift frequency: 3 days per week, 12 hours per day (central tendency, 36 hours/week) or 4 days per week, 12 hours per day (high end, 48 hours per week) (see Section 4.5)
- Annual frequency: 50 weeks per year
- Glove use: Yes, when potential for contact with NMP-containing liquid exists, PF=20 (95%) based on training programs and strict work rules

The refined scenario is considered to be conservative (likely to overestimate exposure) because most container changeout events are expected to result in *de minimis* dermal contact supported by the absence of detectable NMP in air. It is possible, although not likely, that non-routine events could occur resulting in an acute exposure potential somewhat greater than three to ten fingerprints possibly up to a surface area equal to the palm side of both hands. Acute exposures up to the palm side of both hands are evaluated in Section 6.4.2 of this report.

4.9.5 Maintenance

The U.S. EPA assumed a scenario equivalent to one or two hands of immersion in NMP-containing liquid for a 6 hour or a 12 hour shift (30 to 60 hours per week). Cardno ChemRisk notes that the maintenance tasks described in SIA (2019a) represent some potential for dermal contact, but that U.S. EPA has assumed implausibly high contact times and surface areas. NMP was generally not detected in personal air sampling with a maximum detected concentration of 0.99 ppm over a sampling duration of 32 minutes during wet bench annual maintenance. Several factors limit the dermal exposure potential in maintenance activities, including:

- Leak detection and local exhaust ventilation is typically present,
- Filter lines are depressurized and flushed prior to changes,
- NMP potentially associated with hot plates is driven from the resist during the bake step, and
- Performance of parts cleaning in exhausted enclosures.

The frequency of maintenance tasks varies. For example, tool cleaning can be performed a few times per shift to only once per year. This refined analysis assumes maintenance activities occur each shift to

account for variation across workers and facilities, but it should be noted that some maintenance tasks do not occur daily.

The following revisions were made to the maintenance scenario:

- Surface area potentially exposed to NMP-containing liquid: 50% to 70% of the palm side of both hands based on the description of the tasks in SIA (2019a) (see Table 4-1 for areas)
- Daily dermal loading: 0.7 mg/m² (central tendency) and 2.1 (high-end) mg/cm² (see Section 4.2)
- Daily dermal contact time: 20 minutes (central tendency) and 60 minutes (high end)
- Weekly shift frequency: 3 days per week, 12 hours per day (central tendency, 36 hours/week) or 4 days per week, 12 hours per day (high end, 48 hours per week) (see Section 4.5)
- Annual frequency: 50 weeks per year
- Glove use: Yes, when potential for contact with NMP-containing liquid exists, PF=20 (95%) based on training programs and strict work rules

The refined scenario is considered to be conservative (likely to overestimate exposure) because many maintenance tasks do not involve NMP containing liquids. Thus, the assumed frequency of tasks where NMP-containing liquid is assumed to be present is likely conservatively greater than the expected frequency at many facilities. It is possible, although not likely, that non-routine events could occur resulting in an acute exposure potential somewhat greater than 50 to 70% of the palm side of the hand possibly up to a surface area equal to the palm side of both hands. Acute exposures up to the palm side of both hands are evaluated in Section 6.4.2 of this report.

4.9.6 Virgin NMP truck unloading

The U.S. EPA assumed a scenario equivalent to one or two hands of immersion in NMP-containing liquid for a 6 hour or a 12 hour shift (30 to 60 hours per week) for 5 days per week for 52 weeks per year. As noted in SIA (2019a) virgin NMP truck unloading occurs once per year. The task requires sampling and line connection/disconnection. This refined analysis assumes some potential for contact with NMP, limited to the portion of the hand performing the line connection/disconnection or sampling task.

The following revisions were made to the virgin NMP truck unloading scenario:

- Surface area potentially exposed to NMP-containing liquid: 10 fingertips (central tendency) to 50% of the palm, or ten fingers (high end) based on the tasks performed (see Table 4-1 for areas)
- Daily dermal loading: 0.7 mg/m² (central tendency) and 2.1 (high-end) mg/cm² (see Section 4.2)
- Daily dermal contact time: 20 minutes (central tendency) and 60 minutes (high end)
- Weekly shift frequency: 1 day per week (8-hour shift)
- Annual frequency: 1 week per year
- Glove use: Yes, when potential for contact with NMP-containing liquid exists, PF=20 (95%) based on training programs and strict work rules

It is possible, although not likely, that non-routine events could occur resulting in an acute exposure potential somewhat greater than 10 fingertips or 50% of the palm side of the hands possibly up to a surface area equal to the palm side of both hands. Acute exposures up to the palm side of both hands are evaluated in Section 6.4.2 of this report.

4.9.7 Waste truck loading

The U.S. EPA assumed a scenario equivalent to one or two hands of immersion in NMP-containing liquid for a 6 hour or a 12 hour shift (30 to 60 hours per week) for 5 days per week for 52 weeks per year. SIA indicates that waste truck unloading can occur twice per year, once per month or once every three weeks. The task requires sampling, transfer hose operation and removal of residual with pressurized air. This

refined analysis assumes some potential for contact with NMP, limited to the portion of the hand performing the transfer hose placement and pressurization.

The following revisions were made to the waste truck loading scenario:

- Surface area potentially exposed to NMP-containing liquid: 10 fingertips (central tendency) to 50% of the palm, or ten fingers (high end) based on the tasks performed (see Table 4-1 for areas)
- Daily dermal loading: 0.7 mg/m² (central tendency) and 2.1 (high-end) mg/cm² (see Section 4.2)
- Daily dermal contact time: 20 minutes (central tendency) and 60 minutes (high end)
- Weekly shift frequency: 1 day per week (8-hour shift)
- Annual frequency: Once per month (central tendency) or once every three weeks (high-end)
- Glove use: Yes, when potential for contact with NMP-containing liquid exists, PF=20 (95%) based on training programs and strict work rules

It is possible, although not likely, that non-routine events could occur resulting in an acute exposure potential somewhat greater than 10 fingertips or 50% of the palm side of the hands possibly up to a surface area equal to the palm side of both hands. Acute exposures up to the palm side of both hands are evaluated in Section 6.4.2 of this report.

5 Refined Exposure Estimates for Semiconductor Manufacturing

This section presents the results of the refined exposure assessment reflecting the updated scenario parameters presented in Section 4. The updated PBPK model results are presented in a format similar to the format used in the 2019 U.S. EPA draft evaluation.

5.1 Summary of PBPK Modeling Parameters

The updated summary of PBPK modeling parameters for inhalation and dermal vapor is presented in Table 5-1. This table updates U.S. EPA (2019a) Table 2-31, and reflects a typical shift time of 12 hours/day for 3 or 4 days per week. The full-shift TWA is based on samples where a 12 hour shift time was noted with the exception of the truck loading scenarios.

Table 5-1: Summary of PBPK modeling parameters for worker inhalation exposure [updates U.S. EPA (2019a) Table 2-31]

Work Activity	Parameter Characterization	Shift Time	Shift Frequency	Annual Frequency	Number of samples	Full-Shift NMP Air Concentration	Source
		(hours/day)	(days/week)	(weeks/year)		(mg/m ³ , TWA)	
Container handling, small containers	Central tendency (50 th percentile)	12	3	50	14	0.51	SIA, 2019a
	High-end (95 th percentile)	12	4	50		0.61	SIA, 2019a
Container handling, drums	Central tendency (50 th percentile)	12	3	50	10	0.013	SIA, 2019a
	High-end (95 th percentile)	12	4	50		1.6	SIA, 2019a
Typical fab worker	Central tendency (50 th percentile)	12	3	50	28	0.14	SIA, 2019a
	High-end (95 th percentile)	12	4	50		0.41	SIA, 2019a
Fab worker w/ NMP container changeout	Central tendency (50 th percentile)	12	3	50	28	0.14	SIA, 2019a
	High-end (95 th percentile)	12	4	50		0.41	SIA, 2019a
Maintenance	Central tendency (50 th percentile)	12	3	50	36	0.02	SIA, 2019a
	High-end (95 th percentile)	12	4	50		0.70	SIA, 2019a
Virgin NMP truck unloading	Central tendency (50 th percentile)	8	1	1	1	4.8	SIA, 2019a
	High-end (95 th percentile)	8	1	1		4.8	SIA, 2019a
Waste truck loading	Central tendency (Single sample)	8	1	12	1	0.72	SIA, 2019a
	High-end (Single sample)	8	1	17.3		0.72	SIA, 2019a

The updated summary of PBPK modeling parameters for dermal liquid contact is presented in Table 5-2. This table updates U.S. EPA (2019a) Table 2-32, and adds a dermal contact time assumption of 20 minutes (central tendency) or 60 minutes (high-end) based on the IH SkinPerm modeling presented in Section 4.4. This refinement also considers plausible central tendency and high-end surface areas as described in Section 4.9. A glove PF of 20 was selected as discussed in Section 4.1. Dermal liquid contact is assumed to occur at the beginning of the shift for computational simplicity. Cardno ChemRisk made a minor modification to the U.S. EPA PBPK acslX code to facilitate the inclusion of a dermal liquid contact time less than the shift time.

Table 5-2: Summary of worker dermal liquid exposure parameters [updates U.S. EPA (2019a) Table 2-32]

Work Activity	Parameter Characterization	Glove Protection Factor	NMP Weight Fraction	Shift Frequency	Annual Frequency	Skin Surface Area Exposed ^b		Dermal Contact Time	Body Weight
			Unitless	(days/week)	(weeks/year)	Male (cm ²)	Female (cm ²)	(h)	(kg)
Container handling, small containers	Central tendency (50 th percentile)	20	0.6	3	50	24.08	20.03	0.33	74 (f) 88 (m)
	High-end (95 th percentile)	20	0.75	4	50	80.25	66.75	1.00	
Container handling, drums	Central tendency (50 th percentile)	20	0.5	3	50	24.08	20.03	0.33	74 (f) 88 (m)
	High-end (95 th percentile)	20	0.75	4	50	80.25	66.75	1.00	
Typical fab worker	Central tendency (50 th percentile)	20	N/A	3	50	0.0	0.0	0.00	74 (f) 88 (m)
	High-end (95 th percentile)	20	N/A	4	50	0.0	0.0	0.00	
Fab worker w/ NMP container changeout	Central tendency (50 th percentile)	20	0.025	3	50	24.08	20.03	0.33	74 (f) 88 (m)
	High-end (95 th percentile)	20	0.05	4	50	80.25	66.75	1.00	
Maintenance	Central tendency (50 th percentile)	20	0.5	3	50	267.5	222.5	0.33	74 (f) 88 (m)
	High-end (95 th percentile)	20	1	4	50	374.5	311.5	1.00	
Virgin NMP truck unloading	Central tendency (Single sample)	20	1	1	1	80.25	66.75	0.33	74 (f) 88 (m)
	High-end (Single sample)	20	1	1	1	267.5	222.5	1.00	
Waste truck loading	Central tendency (Single sample)	20	0.92	1	12	80.25	66.75	0.33	74 (f) 88 (m)
	High-end (Single sample)	20	0.92	1	17.3	267.5	222.5	1.00	

The refined PBPK model assumptions are presented in Table 5-3 which updates Table 2-33 in the U.S. EPA draft evaluation. This table summarizes the refinements and corrections described in Section 4, Table 5-1 and Table 5-2. Of note, this table includes an appreciably greater amount of detail per work activity than presented in U.S. EPA (2019a) Table 2-33. A concise summary of the PBPK inputs is provided in Table 5-4 updating U.S. EPA (2019a) Table 2-34.

Table 5-3: Explanation of PBPK input parameters [updates U.S. EPA (2019a) Table 2-33]

Work Activity	Scenario	Air Concentration Data	Shift Duration ^a	Exposure Frequency	Gloves	Skin Surface Area Exposed	Dermal Contact Time	NMP Weight Fraction
Container handling, small containers	Central Tendency	Central tendency (50 th percentile) of 12-hr TWA	12 hour shift	Once per shift, three shifts per week, 52 weeks per year	Yes, employees provided with comprehensive glove training	3 fingertips	With a dermal loading of 0.7 mg/cm ² , the evaporation time of NMP is approximately 20 minutes.	Central tendency (50 th percentile)
	High-end	High-end (95 th percentile) of 12-hr TWA		Once per shift, four shifts per week, 52 weeks per year		10 fingertips	With a dermal loading of 2.1 mg/cm ² , the evaporation time of NMP is approximately 60 minutes.	High-end (95 th percentile)
Container handling, drums	Central Tendency	Central tendency (50 th percentile) of 12-hr TWA	12 hour shift	Once per shift, three shifts per week, 52 weeks per year	Yes, employees provided with comprehensive glove training	3 fingertips	With a dermal loading of 0.7 mg/cm ² , the evaporation time of NMP is approximately 20 minutes.	Central tendency (50 th percentile)
	High-end	High-end (95 th percentile) of 12-hr TWA		Once per shift, four shifts per week, 52 weeks per year		10 fingertips	With a dermal loading of 2.1 mg/cm ² , the evaporation time of NMP is approximately 60 minutes.	High-end (95 th percentile)
Typical fab worker	Central Tendency	N/A	12 hour shift	Once per shift, three shifts per week, 52 weeks per year	Yes, employees provided with comprehensive glove training	No dermal exposure to NMP	No dermal exposure to NMP	Central tendency (50 th percentile)
	High-end	N/A		Once per shift, four shifts per week, 52 weeks per year		No dermal exposure to NMP	No dermal exposure to NMP	High-end (95 th percentile)
Fab worker w/ NMP container changeout	Central Tendency	"Photolithography formulations contain <5% NMP and may be NMP free" (SIA, 2019a); 50 th percentile of 0 and 5%	12 hour shift	Once per shift, three shifts per week, 52 weeks per year	Yes, employees provided with comprehensive glove training	No dermal exposure to NMP	With a dermal loading of 0.7 mg/cm ² , the evaporation time of NMP is approximately 20 minutes.	Central tendency (50 th percentile)
	High-end	"Photolithography formulations contain <5% NMP and may be NMP free" (SIA, 2019a); 95 th percentile of 0 and 5%		Once per shift, four shifts per week, 52 weeks per year		No dermal exposure to NMP	With a dermal loading of 2.1 mg/cm ² , the evaporation time of NMP is approximately 60 minutes.	High-end (95 th percentile)
Maintenance	Central Tendency	Central tendency (50 th percentile) of 12-hr TWA	12 hour shift	Once per shift, three shifts per week, 52 weeks per year	Yes, employees provided with comprehensive glove training	50% of the palm side of each hand	With a dermal loading of 0.7 mg/cm ² , the evaporation time of NMP is approximately 20 minutes.	Central tendency (50 th percentile)
	High-end	High-end (95 th percentile) of 12-hr TWA		Once per shift, four shifts per week, 52 weeks per year		70% of the palm side of each hand	With a dermal loading of 2.1 mg/cm ² , the evaporation time of NMP is approximately 60 minutes.	High-end (95 th percentile)

^a The typical duration fab operators and technicians perform work in the fab is 10.5 hours of a 12 hour shift (SIA, 2019a).

Table 5-3 (continued): Explanation of PBPK input parameters [updates U.S. EPA (2019a) Table 2-33]

Work Activity	Scenario	Air Concentration Data	Shift Duration ^a	Exposure Frequency	Gloves	Skin Surface Area Exposed	Dermal Contact Time	NMP Weight Fraction
Virgin NMP truck unloading	Central Tendency	Single value	8 hour shift	Once per year	Yes, employees provided with comprehensive glove training	10 fingertips	With a dermal loading of 0.7 mg/cm ² , the evaporation time of NMP is approximately 20 minutes.	Central tendency (50 th percentile)
	High-end	Single value	8 hour shift	Once per year		50% of the palm side of each hand	With a dermal loading of 2.1 mg/cm ² , the evaporation time of NMP is approximately 60 minutes.	High-end (95 th percentile)
Waste truck loading	Central Tendency	Single value	8 hour shift	Once per month	Yes, employees provided with comprehensive glove training	10 fingertips	With a dermal loading of 0.7 mg/cm ² , the evaporation time of NMP is approximately 20 minutes.	Central tendency (50 th percentile)
	High-end	Single value	8 hour shift	Once every three weeks		50% of the palm side of each hand	With a dermal loading of 2.1 mg/cm ² , the evaporation time of NMP is approximately 60 minutes.	High-end (95 th percentile)

^a The typical duration fab operators and technicians perform work in the fab is 10.5 hours of a 12 hour shift (SIA, 2019a).

Table 5-4: PBPK model input parameters [updates U.S. EPA (2019a) Table 2-34]

Work Activity	Scenario	Full-Shift NMP Air Concentration	NMP Weight Fraction	Shift time	Shift Frequency	Annual Frequency	Glove Protection Factor	Skin Surface Area Exposed		Dermal Contact Time	Body Weight
		(mg/m ³ , TWA)	Unitless	(hours/ day)	(days/ week)	(weeks/ year)		Male (cm ²)	Female (cm ²)	(h)	(kg)
Container handling, small containers	Central Tendency	0.511	0.6	12	3	50	20	24.08	20.03	0.33	74 (f) 88 (m)
	High-end	0.613	0.75	12	4	50	20	80.25	66.75	1.00	
Container handling, drums	Central Tendency	0.013	0.5	12	3	50	20	24.08	20.03	0.33	74 (f) 88 (m)
	High-end	1.557	0.75	12	4	50	20	80.25	66.75	1.00	
Typical fab worker	Central Tendency	0.139	N/A	12	3	50	20	0.00	0.00	0.00	74 (f) 88 (m)
	High-end	0.409	N/A	12	4	50	20	0.00	0.00	0.00	
Fab worker w/ NMP container changeout	Central Tendency	0.139	0.025	12	3	50	20	24.08	20.03	0.33	74 (f) 88 (m)
	High-end	0.409	0.05	12	4	50	20	80.25	66.75	1.00	
Maintenance	Central Tendency	0.020	0.5	12	3	50	20	267.50	222.50	0.33	74 (f) 88 (m)
	High-end	0.696	1	12	4	50	20	374.50	311.50	1.00	
Virgin NMP truck unloading	Central Tendency	4.822	1	8	1	1	20	80.25	66.75	0.33	74 (f) 88 (m)
	High-end	4.822	1	8	1	1	20	267.50	222.50	1.00	
Waste truck loading	Central Tendency	0.715	0.92	8	1	12	20	80.25	66.75	0.33	74 (f) 88 (m)
	High-end	0.715	0.92	8	1	17.3	20	267.50	222.50	1.00	

5.2 Summary of Updated Internal Exposure and MOEs

The updated human PBPK analysis was performed using the U.S. EPA (2019b) code in acslX Version 3.0.2.1. We made minor modifications to the U.S. model input template (an Excel file), .m file (an acslX script file), and the acslX .csl file (the model code file) (See Appendix A). The template was modified to input permeability constant, dermal contact time and days per week of exposure. The script file was modified to read these quantities from the input template, and define NMP density as a static parameter. The code file was modified to differentiate the dermal liquid contact time from the inhalation and dermal vapor exposure time.

The internal exposure analysis presented below is based in the point of departure (POD) determined in the U.S. EPA draft human health hazard assessment. The U.S. EPA (2019a) selected a chronic POD equal to an AUC of 183 hr-mg/L based on reduced male fertility and an acute POD equal to a peak serum concentration (C_{max}) of 216 mg/L. A review of the determination of the POD was not in the scope of this analysis.

Updated AUCs and MOEs for the chronic male scenario are presented in Table 5-5, and updated peak serum concentration and MOEs for the acute female scenario are presented in Table 5-6. Table 5-5 updates U.S. EPA (2019a) Table 4-28 and Table 5-6 updates U.S. EPA (2019a) Table 4-27. The acute and chronic MOEs are greater than 30 indicating safe use of NMP in semiconductor manufacturing scenarios. Chronic MOEs varied from 298 to 48200, and acute MOEs varied from 942 to 60100. As expected due to increased potential for dermal contact with NMP-containing liquids, the lowest high-end chronic and acute MOEs were associated with tool maintenance. Based on the results of this updated analysis, it can be concluded that worker use of NMP in the semiconductor industry does not present an unreasonable risk of injury to health. Potential uncertainties in this analysis are addressed in Section 6 of this report.

Table 5-5: Non-cancer risk estimates for chronic exposure [updates U.S. EPA (2019a) Table 4-28]

Work Activity	Health Effect, Endpoint and Study	Chronic POD, AUC (hr mg/L)	Scenario	Weekly Average Chronic Exposure, AUC	Annual Frequency	Annual Average Chronic Exposure, AUC	Annual Average MOE	Benchmark MOE
				(hr mg/L)		(hr mg/L)		
Container handling, small containers	Reproductive Effects Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.09	50	0.09	2018	30
			High-end	0.22	50	0.21	864	30
Container handling, drums	Reproductive Effects Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.01	50	0.01	31345	30
			High-end	0.44	50	0.43	430	30
Typical fab worker	Reproductive Effects Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.02	50	0.02	7777	30
			High-end	0.10	50	0.09	1983	30
Fab worker w/ NMP container changeout	Reproductive Effects Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.02	50	0.02	7717	30
			High-end	0.10	50	0.10	1883	30
Maintenance	Reproductive Effects Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.05	50	0.04	4151	30
			High-end	0.64	50	0.61	298	30
Virgin NMP truck unloading	Reproductive Effects Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.20	1	0.004	48186	30
			High-end	0.27	1	0.01	34727	30
Waste truck loading	Reproductive Effects Decreased Fertility (Exxon, 1991)	183	Central Tendency	0.04	12	0.01	22160	30
			High-end	0.11	17.3	0.04	5179	30

Note: Exxon, 1991 cited as "Exxon, B. (1991). Project No. 236535, 26 Nov 1991. ((sponsored by GAF Corp., Wayne, USA). (as 7044 cited in OECD, 2007)). Wayne, USA: GAF Corp." in U.S. EPA, 2019a.

Table 5-6: Non-cancer risk estimates for acute exposure [updates U.S. EPA (2019a) Table 4-27]

Work Activity	Health Effect, Endpoint and Study	Acute POD, C_{max} (mg/L)	Scenario	Acute Exposure, Peak Blood Concentration	MOE	Benchmark MOE
				(mg/L)		
Container handling, small containers	Developmental Effects Increased Fetal Resorptions (Saillenfait et al., 2003)	216	Central Tendency	0.02	13107	30
			High-end	0.04	5169	30
Container handling, drums	Developmental Effects Increased Fetal Resorptions (Saillenfait et al., 2003)	216	Central Tendency	0.004	60090	30
			High-end	0.05	4223	30
Typical fab worker	Developmental Effects Increased Fetal Resorptions (Saillenfait et al., 2003)	216	Central Tendency	0.004	48496	30
			High-end	0.01	16931	30
Fab worker w/ NMP container changeout	Developmental Effects Increased Fetal Resorptions (Saillenfait et al., 2003)	216	Central Tendency	0.004	48448	30
			High-end	0.01	16749	30
Maintenance	Developmental Effects Increased Fetal Resorptions (Saillenfait et al., 2003)	216	Central Tendency	0.039	5499	30
			High-end	0.23	942	30
Virgin NMP truck unloading	Developmental Effects Increased Fetal Resorptions (Saillenfait et al., 2003)	216	Central Tendency	0.141	1536	30
			High-end	0.20	1067	30
Waste truck loading	Developmental Effects Increased Fetal Resorptions (Saillenfait et al., 2003)	216	Central Tendency	0.025	8781	30
			High-end	0.15	1417	30

Note: Saillenfait et al., 2003 cited as "Saillenfait, AM; Gallissot, F; Morel, G. (2003). Developmental toxicity of N-methyl-2-pyrrolidone in 7259 rats following inhalation exposure. Food Chem Toxicol 41: 583-588." in U.S. EPA, 2019a.

6 Uncertainty Analysis

The U.S. EPA October 2019 draft evaluation indicates that unreasonable risk determinations for workers using NMP is driven by “reproductive effects from chronic inhalation and dermal exposures” (U.S. EPA, 2019a; p. 21, l. 221-222). Cardno ChemRisk performed a sensitivity analysis using the fab worker classification as an example and found that inhalation and dermal vapor exposures were not meaningful determinants in the U.S. EPA unreasonable risk determination. The appreciable contribution of the dermal liquid contact pathway to the risk determination supports the development and execution of a refined analysis for this pathway with a more detailed consideration of the industry conditions of use than was provided in the October 2019 draft evaluation (U.S. EPA, 2019a). Cardno ChemRisk updated the U.S. EPA assessment to include a more detailed consideration of the industry conditions of use and found no unreasonable risk for workers using NMP in the semiconductor manufacturing industry. This section evaluates the uncertainties in the conclusion of the refined analysis, and presents a discussion of specific key determinates of exposure potential.

6.1 General Discussion

Cardno ChemRisk performed a sensitivity analysis to evaluate the U.S. EPA statement that chronic inhalation and dermal exposures contributed to the determination of unreasonable risk. As discussed in Section 3, inhalation and dermal vapor exposures contribute negligibly to the unreasonable risk determination, with the majority of the peak serum concentration or AUC determined by the liquid available for direct contact with the skin or gloves (as well as duration of contact). Airborne concentrations of NMP are well below the OEL derived in Poet et al. (2016), or an equivalent OEL that could be derived based on the U.S. EPA revised POD and benchmark MOE. It can be concluded that uncertainty in the assumptions associated with airborne concentrations of NMP does not affect the conclusions of unreasonable risk. Thus, the primary focus of this uncertainty analysis is on the contact of NMP-containing liquid with worker skin.

As part of the uncertainty analysis, Cardno ChemRisk assessed the weight of evidence, which indicates that dermal liquid contact is unlikely to be the dominant source of NMP for workers in the semiconductor industry for the following reasons:

- Industrial hygiene information provided by SIA (2019a) indicated a low potential for exposure to NMP based well-described work and maintenance practices supported by air sampling data. This data indicated a low detection frequency of NMP with a suitably low detection limit (generally less than 1 ppm as compared NMP saturated vapor concentration of approximately 400 ppm at ambient temperature) to detect dispersive uses of the solvent or large surfaces with residual NMP. The low NMP concentrations at semiconductor facilities during routine or maintenance tasks are not indicative of the presence of liquid NMP, and therefore are inconsistent with EPA’s assumption of extensive dermal contact.
- Task descriptions provide by SIA (2019a) show that there are generally limited opportunities for skin contact with NMP-containing liquid based on the SIA work descriptions. A limited number of maintenance tasks have a higher potential for dermal contact with residual NMP. However, operational conditions and engineering controls, such as flushing of NMP from filters prior to filter changes, limit the opportunity for contact with residual NMP. Additionally, in maintenance operations where there is a potential for contact with residual NMP, the technician wears PPE including gloves. The selection of PPE, donning, use and training is performed under specific procedures in the semiconductor industry,
- Strict work rules and procedures in the semiconductor industry indicate that the glove PF for specific activity training of 20 (95% efficiency) is appropriate,
- In contrast to the U.S. EPA draft evaluation where dermal liquid contact dominated internal exposure, Poet et al. (2016) describes the dermal liquid pathway as typically providing only “some contribution” to internal exposure, with inhalation identified as the primary route, and

- Consensus reviews of NMP (e.g. EC SCCS, 2011) note that prolonged skin contact with NMP can cause dermatitis, blistering or cracking of skin, thus indicating that the prolonged contact (one or two hands immersed in solvent for 30 or 60 hours per week, respectively) assumed in the U.S. EPA screening analysis is implausible.

Taken together, the weight of evidence analysis indicates that internal exposures from contact with NMP-containing liquid are unlikely to substantiate an unreasonable risk determination. This conclusion was further evaluated by examining uncertainty in the specific factors that contribute appreciably to internal exposures from the dermal liquid contact pathway.

6.2 Specific Factors

6.2.1 Loading and contact time

Uncertainty in loading and contact time were addressed by using lower and upper bound loading estimates based on prior U.S. EPA research and AIHA recommendations. The central tendency estimate was based on the lower bound of the AIHA recommendation because in many cases no contact with NMP-containing liquid occurs, and when it does occur, the amount of residue is expected to be minimal. The upper bound loading was set to the upper bound of the range recommended by AIHA. Contact time was estimated based on a time to complete evaporation for each loading estimate, with the higher loading estimated suggesting up to one hour of contact time.

6.2.2 Glove protection factor

The strict work rules in the industry and training programs support a glove PF of 20 (95%). The U.S. EPA draft assessment defaults to lower PF of 10 (90%) associated with “basic” training. The impact of lowering the MOE to 10 was evaluated for the high-end chronic maintenance worker scenario, which represented the lowest annual average MOE. As shown in Table 6-1, use of a lower PF did not impact the conclusion of this assessment that NMP does not present an unreasonable risk.

Table 6-1: MOE by glove PF for maintenance worker chronic scenario

Scenario	Glove PF	Annual Average AUC (h-mg/L)	MOE	Benchmark MOE	Conclusion
Maintenance, High End, Glove use = yes	20	0.61	298	30	Does not present an unreasonable risk
Maintenance, High End, Glove use = yes	10	1.07	171	30	Does not present an unreasonable risk

6.2.3 Liquid permeability constant

As noted in Section 4.7, it appears to have been the intent of U.S. EPA to use a slightly higher PVL for neat as compared to dilute NMP. Often times, prolonged contact with solvents can denature the cellular structure of the skin, thus increasing the apparent permeability to a level greater than predicted by theoretical considerations. Cardno ChemRisk used the lower permeability constant in the refined assessment because prolonged contact with NMP is unlikely.

Cardno ChemRisk evaluated the impact of using the higher permeability constant proposed by U.S. EPA for neat NMP for the manufacturing scenario. As shown in Table 6-2, 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.

Table 6-2: MOE by PVL for maintenance worker chronic scenario

Scenario	PVL (cm/h)	Annual Average AUC (h-mg/L)	MOE	Benchmark MOE	Conclusion
Maintenance, High End, Fraction = 100%	4.78x10 ⁻⁴	0.61	298	30	Does not present an unreasonable risk
Maintenance, High End, Fraction = 100%	2.05x10 ⁻³	2.12	86	30	Does not present an unreasonable risk

6.2.4 Surface area

A range of surface areas of potential contact with NMP-containing liquid was determined based on the descriptions of the tasks provided in SIA (2019a) and additional clarification provided by SIA. There were no task descriptions that suggested that the surface of one or two hands would be immersed in NMP for prolonged periods. Additional feedback from SIA representatives indicated that in typical cases little to no direct contact with NMP was likely to occur, but that some maintenance activities potentially presented an opportunity for contact with a portion of the palm side of the hand. The highest surface area considered in the refined assessment was 70% of the palm side of two gloved hands in maintenance tasks. It is important to note that this estimate likely overestimates the chronic exposure potential appreciable, as this level of exposure would not occur routinely. Additional feedback from the industry indicated that it is possible that under non-routine conditions (e.g. one or less times per year), it is possible, but not likely that the full palm side of each gloved hand could contact NMP. It would not be appropriate to consider this atypical level of glove contact to occur chronically. Thus, a supplemental acute scenario was performed to assess the acute MOE for a plausible acute worst case representing an atypical or upset condition where 100% NMP contacted the palm side of two gloved hands. As shown in Table 6-3, there is not an unreasonable risk in the unlikely event that neat NMP were to contact the palm side of two gloved hands.

Table 6-3: Plausible acute worst case

Scenario ^a	Surface Area (cm ²)	Acute Exposure, Peak Blood Concentration (mg/L)	MOE	Benchmark MOE	Conclusion
Central tendency Acute, Fraction = 100%, Loading = 0.7 mg/cm ² , Glove use = yes, PF=20	445 (palm side, two hands)	0.16	1372	30	Does not present an unreasonable risk
High End Acute, Fraction = 100%, , Loading = 2.1 mg/cm ² , Glove use = yes, PF=20	445 (palm side, two hands)	0.52	416	30	Does not present an unreasonable risk

^aAir concentration was set to 0.13 and 1.2 mg/m³ based on the median and 95th percentile of the SIA (2019a) data corresponding to a 12-hour shift time. The estimated MOE is not sensitive to the airport concentration assumptions.

In summary, a consideration of the weight of evidence and specific exposure factors supports the conclusion that NMP does not present an unreasonable risk, and that uncertainty in the model estimates was reasonably addressed in this assessment. Uncertainty in the refined analysis was also addressed by the selection of precautionary exposure scenario parameters. For example, the maintenance scenarios assumed NMP contact during every shift, for the central tendency estimate, however, the opportunity for NMP contact at some facilities may appreciably less frequent.

7 Conclusion

Cardno ChemRisk reviewed the U.S. EPA's use of a physiologically based pharmacokinetic (PBPK) model to prepare an occupational exposure evaluation of semiconductor manufacturing workers. This review included an evaluation of the U.S. EPA approach, as well as the preparation of a refined exposure assessment and risk characterization for semiconductor manufacturing workers based on a critical evaluation of the conditions of use in the industry. Our review included a consideration of the scientific standards of "best available science" and "weight of the scientific evidence" under TSCA. Our review determined that while many aspects of the 2019 U.S. 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.

Our qualitative and quantitative sensitivity analysis showed that of the three pathways (inhalation, dermal vapor and dermal liquid), the only pathway contributing meaningfully the U.S. EPA unreasonable risk determination for use of NMP in the semiconductor manufacturing industry was dermal liquid contact. Our review of the U.S. EPA assumptions for semiconductor manufacturing found that the agency assumed prolonged liquid contact of one or two hands for 30 or 60 hours per week, respectively, under conditions equivalent to immersion in concentrated (generally >50% for most scenarios) or neat NMP. We concluded that this assumption did not represent a plausible central tendency (e.g. median) or high-end (e.g. 95th percentile) condition of use for the semiconductor industry based on the description of the tasks that had been provided by SIA (2019a) to the U.S. EPA.

We found in our review that the data provided by the semiconductor industry and current industrial hygiene dermal modeling guidance available from the American Industrial Hygiene Association (AIHA) provide readily available tools and information for refined dermal contact assessment. Cardno ChemRisk applied the information from SIA, the AIHA IH SkinPerm model and AIHA dermal exposure assessment guidance to prepare refined internal exposure estimates and MOEs for the semiconductor manufacturing scenarios. We found that refinement of the semiconductor manufacturing scenarios resulted in a conclusion that use of NMP in the semiconductor manufacturing industry does not present an unreasonable risk, which was supported by a review of the weight of evidence and an uncertainty analysis.

In summary, our review found that the draft finding of the U.S. EPA concluding unreasonable risk for the use of NMP in semiconductor manufacturing reflected the lack of refinement and use of incorrect assumptions in the screening scenarios (one or two hands immersed in concentrated or neat NMP for 30 or 60 hours per week), rather than a characterization of the current conditions of use in the industry. Cardno ChemRisk reviewed the information provided by SIA (2019a), along with additional supplementary information on the conditions of use, and developed refined exposure estimates for each semiconductor manufacturing scenarios. This analysis indicates a differentiation on exposure potential between jobs, with some functions having no opportunity for dermal direct contact. The resultant acute and chronic MOEs were greater than 30 indicating support for a conclusion that use of NMP in the semiconductor industry does not present an unreasonable risk.

8 References

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Appendix A Updated U.S. EPA NMP PBPK Code

This Appendix presents modifications to the U.S. EPA PBPK code implemented to facilitate this review. The edits include:

- Section A.1: Edits in bold in .csi file included to set dermal liquid contact time,
- Section A.2: Edits in bold in .m file included to set dermal liquid contact time, PVL and density,
- Section A.3: Modified U.S. EPA spreadsheet scenario template for chronic exposures, and
- Section A.4: Modified U.S. EPA spreadsheet scenario template for acute exposures.

A.1 U.S. EPA NMP PBPK Model Code Modified by Cardno ChemRisk (.csl)

```

1 PROGRAM NMPhumPG.ACSL
2
3 !PBPK MODEL FOR N-METHYL PYRROLIDONE in pregnant women
4
5 !T.S. POET,P HINDERLITER. CHEMICAL DOSIMETRY GROUP, PNNL, RICHLAND, WA
6 !First Created 8.8.08
7 !FINAL REPORT FROM INITIAL rat MODEL DEVELOPMENT SUBMITTED 9.02
8 !MODEL CONFIGURED FOR INHALATION (OPEN, WHOLE BODY/NOSE ONLY)
9 ! IV, ORAL, DERMAL, AND IP ROUTES OF ADMINISTRATION.
10 !MODEL TRACKS DISPOSITION OF NMP AND 5-HNMP.
11 !ASSUMPTIONS:
12 ! (1) FLOW-LIMITED (ALL COMPARTMENTS)
13 ! (2) METABOLISM OF NMP BY A sat PATHWAY TO FORM 5HNP
14 ! (3) METABOLISM OF HNP BY SATURABLE PATHWAY TO ETC.
15 ! (5) METABOLISM OCCURS ONLY IN THE LIVER
16 ! (6) TISSUE:BLOOD PART. COEFF. RAT = HUMAN = KRISHNAN EQN
17 !           updated in cmd file to measured in-house
18 ! (7) 5HNP ELIMIN FROM MIXED VENOUS - 1ST ORDER
19 !           THIS DIFFERS FROM 02: URINE BY *GFR CLEARANCE FROM KIDNEY
20 ! METAB RATE CONST. FROM REPORT - UPDATED WITH LIT VALUES in cmd file
21 ! Other parameters changed nominally to harmonize with fetal IPA model of
22 ! Gentry et al. Regu Tox Pharm 36:51-68, 2002
23 ! Gentry model notes:
24 ! -Coding for pregnancy is from MeHgFat.CSL with some minor changes
25 ! -Physiological parameters are from MeHgFat.CSL (ajusted as needed)
26 ! -Non-pregnant mammary tissue and uterine volume is from ICRP
27 ! -Non-pregnant mammary tissue and uterine blood flows are based on the
28 ! - ratios of mammary and uterine tissue volumes to rapidly perfused
29 ! - tissue volume and blood flow to rapidly perfused tissue where rapidly
30 ! - perfused tissue includes liver, lung, etc.
31 ! - ((VMamC/VRapC)*QRapC) and ((VUtrC/VRapC)*QRapC)
32 ! -Data used to fit curve for growing rapidly perfused tissue in
33 ! - MeHgFat.CSL was refit separately to fit curves for growing uterus
34 ! - and mammary tissue in this model
35 ! -Body weight and cardiac output are calculated as the initial values
36 ! - plus the change in the growing compartments
37 ! -Increase in blood flow to fat, mammary tissue, and uterus are modeled
38 ! - as being proportional to the increase in volume in those compartments
39 ! - based on the data in Thoresen and Wesche, 1988 (uterus and mammary
40 ! - tissue)
41 !
42 ! Further updates by Paul Schlosser, US EPA in August 2013 and September 2014
43
44
45 INITIAL
46 ! table reslV, 1, 2881 / 2881*0.0, 2881*0.0 /

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```

47
48 ! Human Total Pulmonary Ventilation Rate (L/hr for 1 kg animal)
49   CONSTANT   QPC = 27.75
50
51 ! Human Blood Flows (fraction of cardiac output)
52   CONSTANT   QCC = 12.9      ! Cardiac output (L/hr for 1 kg animal)
53   CONSTANT   QFatC = 0.052   ! Fat (non-pregnant female)
54   CONSTANT   QLivC = 0.227   ! Liver
55   CONSTANT   QMamC = 0.027   ! Mammary tissue (non-pregnant female)
56   CONSTANT   QRapC = 0.325   ! Rapidly perfused
57   CONSTANT   QSkC = 0.058   ! Skin
58   CONSTANT   QUtrC = 0.0062  ! Uterus (non-pregnant female)
59
60 ! Permeability-Area Product (L/hr)
61   CONSTANT   PAFC = 0.01     ! Diffusion on fetal side of placenta from Gentry
62
63 ! Human Tissue Volumes (fraction of body weight)
64   CONSTANT   BWInit = 67.8    ! Pre-pregnancy body weight (kg)
65   CONSTANT   VALvC = 0.0079   ! Alveolar blood
66   CONSTANT   VBLC=0.06
67   CONSTANT   VFatC = 0.273    ! Fat (non-pregnant female)
68   CONSTANT   VLivC = 0.026    ! Liver
69   CONSTANT   VMamC = 0.0062   ! Mammary tissue (non-pregnant female)
70   CONSTANT   VRapC = 0.1044   ! Rapidly perfused
71   !CONSTANT   VSlwC              ! Slowly perfused is calculated below
72   CONSTANT   VUtrC = 0.0014   ! Uterus (non-pregnant female)
73   CONSTANT   VSKC=0.19
74
75 ! Human Dermal Exposure Parameters
76   CONSTANT   P = 0.0016       ! Permeability constant (Kp) (cm/hr)
77   CONSTANT   PV=31.0          ! PERMEABILITYT CONSTANT (CM/HR) FOR VAPOR
78
79 !FOR PARENT MODEL, SKIN COMPARTMENT IS ONLY DEFINED AS DOSED SKIN
80   CONSTANT   SAL = 0.01       !SURFACE AREA EXPOSED to liquid, SQ.CM
81   CONSTANT   SAVc = 0.25      !fraction SURFACE AREA EXPOSED to gas/vapor, SQ.CM
82   CONSTANT   amask = 0.03
83   CONSTANT   HT=170.0         !height (or length) of reference man
84   TSA = 71.81*(BWinit**0.425)*(HT**0.725)!for humans, DuBois and DuBois, 1916, as reported in Reference Man
85   SAV = SAVC*TSA              ! SURFACE AREA EXPOSED to gas/vapor, SQ.CM
86   VSKIC = VSKC*SAI/TSA
87   QSKIC = QSKC*SAI/TSA
88   VSKvC = VSKC*SAv/TSA
89   QSKvC = QSKC*SAv/TSA
90
91   CONSTANT FAD = 0.0 !FRACTION ABSORBED - FROM BADER ET AL, CALCULATE FROM AMNT REMAINING
92   ON GAUZE
93   CONSTANT PVL=0.0
94

```

95 ! Slowly perfused (defined as balance of tissues and flows)
96 $V_{SlwC} = 0.91 - (V_{FatC} + V_{LivC} + V_{MamC} + V_{RapC} + V_{UtrC} + V_{SKvC} + V_{SKIC})$
97 ! NOTE: 0.91 IS APPROX WHOLE BODY LESS BONE
98 $V_{SLwC5} = 0.91 - (V_{FatC} + V_{LivC} + V_{RapC})$
99 $Q_{SlwC} = 1.0 - (Q_{FatC} + Q_{LivC} + Q_{MamC} + Q_{RapC} + Q_{UtrC} + Q_{SKvC} + Q_{SKIC})$
100 $Q_{SLwC5} = 1.0 - (Q_{FatC} + Q_{LivC} + Q_{RapC})$
101
102 ! Molecular Weights
103 CONSTANT MW=99.13 !MOL. WT. NMP, MG/MMOL
104 CONSTANT MW1= 116.14 !MOL. WT. 5-HNP, MG/MMOL
105
106 Stoch = MW1/MW
107
108 ! Human NMP/Blood Partition Coefficients
109 !EXPERIMENTALLY MEASURED RATVALUES
110 CONSTANT PB = 450.0 ! Blood/air
111 CONSTANT PFat = 0.61 ! Fat
112 CONSTANT PLiv = 1.00 ! Liver
113 CONSTANT PMam = 1.0 ! Mammary tissue, estimated from liver
114 CONSTANT PPla = 0.31 ! Placenta
115 CONSTANT PRap = 1.0 ! Rapidly perfused tissue, liver
116 CONSTANT PSlw = 0.30 ! Slowly perfused tissue, muscle
117 CONSTANT PUtr = 0.34 ! Uterus
118 CONSTANT PSKA = 44.5 ! use (blood/air)*(rat skin:liquid)/(human blood:liquid)
119 CONSTANT PSKL = 0.42 ! MEASURED SKIN;LIQUID (rat)
120 constant pskb = 0.099 ! (rat skin:liquid)/(human blood:liquid)
121 CONSTANT PLU= 0.1 ! LUNG:BLOOD
122
123 !METABOLIC RATE CONSTANTS
124 !**THESE ARE FROM PAYAN ET AL
125 !NMP TO 5HNP
126 CONSTANT Af1 = 0.0112 ! AFFINITY CONSTANT, I/MG
127 CONSTANT VK1C = 0.4663 ! V_{maxc}/K_m , 1/(hr * $BW^{0.75}$)
128
129 ! Human 5HNMP volume of distribution
130 CONSTANT VOD5Hc = 0.3 ! VOLUME-OF-DISTRIBUTION
131 $VOD5H = VOD5Hc * BW_{init}$
132 !No fetal compartment for metabolite, NMP is considered the active moiety
133
134 !5HNP TO OTHER METABS
135 ! CONSTANT KM2=22.8 !MICHAELIS CONSTANT, MG/L
136 ! CONSTANT VMAX2C=1.0 !MAX. ENZ. ACT., MG/HR/L
137 CONSTANT VK2C=0.0326 ! V_{MAX2C}/K_{M2} , since clearance ~ liner 1/(hr* $kg^{0.75}$)
138 ! Human Uptake and Clearance Parameters
139 !URINARY ELIMINATION OF 5-HNMP - CLEARED FROM BLOOD
140 !note first order rate commented out, saturable fits better
141 CONSTANT KAS=5.0
142 CONSTANT KME=3.83 !First-order constant for 5HNMP in urine (L/hr)

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143     CONSTANT KUMNE=0.182           !First-order CONSTANT FOR NMP IN URINE (L/hr)
144
145 ! Initialize Human Concentrations in Tissues (mg/L)
146     CONSTANT ICArt = 0.0           ! Blood
147     CONSTANT ICFat = 0.0           ! Fat
148     CONSTANT ICLiv = 0.0           ! Liver
149     CONSTANT ICRap = 0.0           ! Rapidly perfused
150     CONSTANT ICSkn = 0.0           ! Skin
151     CONSTANT ICSlw = 0.0           ! Slowly perfused
152     ICMam = ICSlw                   ! Mammary tissue
153     ICUtr = ICRap                   ! Uterus
154
155 ! Dosing Parameters
156     CONSTANT Concppm = 0.0           ! Inhaled concentration (ppm)
157     CONSTANT CONCMGM = 0.0         ! Inhaled concentration (mg/m3)
158     CONSTANT IVDose = 0.0           ! IV dose (mg/kg)
159     CONSTANT PDose = 0.0           ! Oral dose (mg/kg)
160         constant PDose2=0.0
161         constant PDose3=0.0
162     CONSTANT PDrink = 0.0           ! Drinking water dose (mg/kg/day)
163     CONSTANT TChng = 24.0           ! Length inh. exposure or IV inj.(hrs)
164     CONSTANT DaysWk = 5.0           ! Number of exposure days per week
165     CONSTANT TMax = 24.0           ! Maximum time for exposures
166     CONSTANT s2=0.0                !INHALATION ON
167     CONSTANT p2=3.0                !INHALATION EXPOSURE
168     CONSTANT S3=3.16               !INHALTION RESUME (HANOVER STUDY)
169     CONSTANT P3=3.0                !SECOND DAILY EXPOSURE PERIOD
170     constant on3=1.0 ! Set to zero to turn off 2nd daily pulse;
171     constant fullweek=168.0         ! hrs in a fullweek
172     hrsweek=24.0*DaysWk            ! hrs/week in workplace
173
174 ! STARTDS IS ADDED TO TCHNG TO ALLOW FOR DOSING THAT DOES NOT START AT T=0
175 !INITIAL EXPOSURE CONDITIONS
176 !DERMAL
177     CONSTANT CONCL = 0.0           !CONC OF NMP IN LIQUID, MG/L
178     ! Cardno edit start
179     CONSTANT LIQUIDTIME = 0
180     ! Cardno edit end
181
182     constant srate = 0.0             ! mg/hr delivered to skin by spray application
183     CONSTANT VLIQ0 = 1.0e-99        !INITIAL VOLUME APPLIED, L
184     CONSTANT DENSITY=1.02e6 !       Density (mg/L) @ 40C, ~ skin temperature
185     CONSTANT RESID=0.0              !AMOUNT STICKING TO EXPOSURE SYSTEM, MG
186         constant BRUSH=0.0           ! Set to 1.0 for brush/liquid exposure
187     DDN = (CONCL - 1.0)*VLIQ0*FAD ! Subtract 1 mg/L, ~ 1 ppm, from initial conc. to avoid VLIQ --> 0
188     AH20 = (DENSITY+1.0-CONCL)*VLIQ0 ! ... and add it to H20.
189 ! Note, for application of 100% NMP, it is not possible for CSURF to drop below 100%.
190 ! 100% NMP is not diluted in anything, so the "solution" can't become less dilute.

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191 ! The volume (VLIQ) would actually decrease until it's all absorbed.
192 ! Unless the experiment runs long enough for 100% absorption, treat VLIQ as
193 ! extremely large, ~ 10^9, for 100% NMP.
194 ! But check that you don't predict more absorption than was actually applied!
195
196 !IN VITRO HUMAN VAN DYK ET AL. AIHA J 56: 651-660
197 !START WITH SMALL SA SO VSKE IS NON-ZERO (USED IN DENOMINATOR OF CSK CALCULATION)
198
199
200 ! Exposure Conditions Based on User Defined Initial Amounts of Chemical (mg)
201 IF (concppm.EQ.0.0) THEN
202     concmg=concmgm/1000.0                                !CONCERT MG/M3 to mg/L
203 ELSE
204     CONCMg = CONCPpm*MW/24451.    !Convert ppm to mg/Liter!
205 ENDIF
206
207 !CONSTANT CONCMG=0                                !HANNOVER STUDY UNIT MG/M3 SO CONCMG /1000(l/M3)
208 CONSTANT DOSEINTERVAL=24.0                        !TIME BETWEEN DAILY DOSES
209
210 ! Simulation Control Parameters
211 CONSTANT StartDs = 0.0    ! Time first dose is given (hrs)
212 CONSTANT TStop = 6480.0    ! Run simulation for about 9 months
213 CONSTANT CIntC = 0.1
214     CONSTANT    GDstart = 0.0    ! Gestation day on which simulation starts
215
216 ! Scaled Human Pulmonary Ventilation Rate (L/hr)
217     QP = QPC * (BWInit**0.75)
218     QAlv = 0.67 * QP
219
220 ! Scaled Human Blood Flows (L/hr)
221     QCInit = QCC * (BWInit**0.75)
222     QFatI = QFatC * QCInit
223     QLiv = QLIVC * QCInit
224     QMamI = QMamC * QCInit
225     QPlal = 58.5 * VPlal    ! value for 'days'=0 per calculation below
226     QRap = QRapC * QCInit
227     QSlw = (QSlwC * QCInit) - QPlal
228     QUtrI = QUtrC * QCInit
229     QSkI = QSKIC * QCInit
230     QSkv = QSKvC * QCInit
231
232
233 ! Scaled Human Tissue Volumes (L)
234     VAlv = VAlvC * BWInit
235     VFatI = BWInit*(VFatC+(0.09*exp(-12.90995862*exp(-0.000797*24.0*GDstart))))
236     VFetI = 3.50 * (exp(-16.081*exp(-5.67e-4*24.0*GDstart))+ exp(-140.178*exp(-7.01e-4*24.0*GDstart)))
237     VMamI = BWInit*(VMamC+(0.0065*exp(-7.444868477*exp(-0.000678*24.0*GDstart))))
238     VPlal = 0.85*exp(-9.434*exp(-5.23e-4*24.0*GDstart))

```

```

239  VUtrl = BWInit*(VUtrC+(0.02*exp(-4.715669973*exp(-0.000376*24.0*GDstart))))
240  VLiv = VLivC * BWInit
241  VRap = VRapC * BWInit
242  VSKl = VSKlC * BWinit
243  VSKv = VSKvC * BWinit
244  VBL=VBLC * BWINIT
245  VSlw = (VSlwC * BWInit)
246
247  ! Scaled Human Metabolism Parameters
248      VK1 = VK1C * (BWInit**0.75)
249      VK2 = VK2C * (BWInit**0.75)
250  ! Initialize Human NMP Amounts in Tissues
251      IAArt = ICArt * VALv
252      IAFat = ICFat * VFatI
253      IALiv = ICLiv * VLiv
254      IAMam = ICMam * VMamI
255      IARap = ICRap * VRap
256      IASkl = ICSkn * VSKl
257      IASkv = ICSkn * VSKv
258      IASlw = ICSlw * VSlw
259      IAUtr = ICUtr * VUtrl
260  InitTot = IAArt + IAFat + IALiv + IAMam + IARap + IASkl + IASkv + IASlw + IAUtr
261
262
263  ! Initialize Starting Values
264      BW = BWInit
265      Drink = (PDrink * BW) / 24.0    ! Drinking water dose (mg/hr)
266      CINT = CIntC
267      IV = 0.0
268      DayExp = 1.0
269      Clnh = 0.0
270      CONSTANT FRACIN = 0.97    !FRACTIONAL UPTAKE OF NMP BY INHAL,START AT 65%
271                                  !of alveolar - as in Akesson et al 1997
272      CONSTANT FRACOR = 1.0    !FRACTION ABSORBED ORALLY, INITALLY 100%
273
274  ! Convert oral dose from ug/kg to umoles
275  ! Modify dose to account for fractional absorption
276  ODOSE=0.0    ! Initial value
277  ODOSE1= PDOSE * BW * FRACOR    ! umoles
278  ODOSE2= PDOSE2* BW * FRACOR    ! umoles
279  ODOSE3= PDOSE3* BW * FRACOR    ! umoles
280
281  CONSTANT TIME=0.0
282  CONSTANT TIME1 = 0.0 !'daily rat expo (hr)'
283  CONSTANT TIME2 = 4.0 !'SECOND DAILY EXPOSURE (hr)'
284  CONSTANT TIME3 = 4.0 !'THIRD DAILY DOSE'
285  CONSTANT REPTM=720.0    ! CHANGE TO 24 FOR DAILY DOSING
286

```

```

287 SCHEDULE DOSE1 .AT. TIME1
288
289 DZONE = 1.0      ! Start with dermal and fixed conc inhalation exposure on
290 schedule offd.at.p2
291 schedule OND2.at.24.0
292 if (ON3) schedule OND3.at.s3
293
294 END              ! End of Initial
295
296 DYNAMIC
297   ALGORITHM IALG = 2      ! Gear stiff method
298
299 DISCRETE DOSE1
300 ODOSE = ODOSE+ODOSE1
301 SCHEDULE DOSE2 .AT. (TIME+TIME2)
302 END
303
304 DISCRETE DOSE2
305 ODOSE = ODOSE+ODOSE2
306 SCHEDULE DOSE3 .AT. (TIME+TIME3)
307 END
308
309 DISCRETE DOSE3
310 ODOSE = ODOSE+ODOSE3
311 SCHEDULE DOSE1 .AT. (TIME+REPTM-TIME2-TIME3)
312 END
313
314 DISCRETE DoseOn  ! Start dosing
315   INTERVAL DoseInt = 24.0      ! Interval to repeat dosing
316   SCHEDULE DoseOff .AT. T + TChng
317   IF ((T.GE.StartDs) .AND. (T.LT.TMax)) THEN
318       IF (T.LE.(StartDs+TChng)) THEN
319           IF (IVDose.GT.0.0) CINT = MIN(CIntC, (TChng/10.0))
320           IV = (IVDose*BW) / TChng  ! Rate of intravenous dosing (mg/hr)
321       ENDIF
322   ENDIF
323 END ! DoseOn
324
325 DISCRETE DoseOff
326   CInh = 0.0
327   CINT = CIntC
328   IV = 0.0
329 END
330
331 discrete OND2
332   DZONE=1.0
333   SCHEDULE OND2.AT.(T+24.0)
334   SCHEDULE OFFD.AT.(T+P2)

```

```

335  END
336
337  discrete OND3
338      DZONE=1.0
339      SCHEDULE OND3.AT.(T+24.0)
340      SCHEDULE OFFD.AT.(T+P3)
341  END
342
343  !EXPOSURE CONTROL
344  DISCRETE OFFD
345      DZONE=0.0      !TURN OFF DERMAL & FIXED CONC INHALATION
346  END
347
348  DERIVATIVE
349      Hours = T
350      Minutes = T * 60.0
351      Days = T / 24.0 + GDstart
352      Gtime = T + GDstart*24.0
353
354  ! Volume of human fat (L)
355      VFat = BWInit*(VFatC+(0.09*exp(-12.90995862*exp(-0.000797*Gtime))))
356
357  ! Volume of human fetus (L)
358      VFet = 3.50 * (exp(-16.081*exp(-5.67e-4*Gtime))+ exp(-140.178*exp(-7.01e-4*Gtime)))
359
360  ! Volume of human mammary tissue (L)
361      VMam = BWInit*(VMamC+(0.0065*exp(-7.444868477*exp(-0.000678*Gtime))))
362
363  ! Volume of human placenta (L)
364      VPla = 0.85*exp(-9.434*exp(-5.23e-4*Gtime))
365
366  ! Volume of human uterus (L)
367      VUtr = BWInit*(VUtrC+(0.02*exp(-4.715669973*exp(-0.000376*Gtime))))
368
369  ! Increase in human body weight (kg)
370      BW = BWInit + (VFat - VFatl) + VFet + (VMam - VMaml) + VPla + (VUtr - VUtrl)
371
372  ! Scaled human alveolar ventilation (L/hr)
373      QP = QPC * (BW**0.75)
374      QAlv = 0.67 * QP
375
376  ! Increase in human blood flows (L/hr)
377      QFat = QFatI * (VFat / VFatl)
378      QMam = QMamI * (VMam / VMaml)
379      QUtr = QUtrI * (VUtr / VUtrl)
380
381  ! Human Blood flow to placenta (L/hr)
382      QPla = 58.5 * VPla

```

```

383
384 ! Increased human cardiac output (L/hr)
385     QC = QCInit + (QFat - QFatI) + (QMam - QMamI) + (QPla - QPlal) + (Qutr - QUtrl)
386         QSlw5 = Qc - (QFat + QLiv + QRap)
387         VSlw5 = BW - (VFat + VLiv + VRap)
388
389 ! Scaled permeability-area product
390     PAF = PAFC * (VFet**0.75)
391
392 ! ----- HUMAN NMP MODEL -----
393
394 ! Amount Exhaled (mg)
395     RAExh = QAlv * CAIv
396     AExh = INTEG(RAExh, 0.0)
397
398 !CI = concmg*czone + RESLVL(T) !Unice
399 CI = concmg*czone
400 ! for a 5 day/wk exposure, change first pulse to pulse(0,7*24,5*24)
401 ! for daily, pulse(0,1e6,24)
402
403     TORAL= ODOSE1 - AO      !AMT ABSORBED ORALLY, MG!
404 RSTOM = -KAS*AO
405 RAO = KaS*AO  ! Change in stomach (umole/hr)
406 AO=ODOSE1+INTEG(Rstom,0.0)  ! Amt in stomach (umole)
407
408 ! Amount in Fat (mg)
409     RAFat = QFat * (CArt - CVFat)
410     AFat = INTEG(RAFat, IAFat)
411     CFat = AFat / VFat
412     CVFat = CFat / PFat
413
414 ! Amount in Fetus (mg)
415     RAFet = PAF * (CPla - CFet)
416     AFet = INTEG(RAFet, 0.0)
417     CFet = AFet / VFet
418     AUCCFet = INTEG(CFet, 0.0)
419
420 ! Amount in Liver (mg)
421     RALiv = (QLiv * (CArt - CVLiv)) + RAO + Drink - RAMet1
422     ALiv = INTEG(RALiv, IALiv)
423     CLiv = ALiv / VLiv
424     CVLiv = CLiv / PLiv
425
426 ! Amount Metabolised in Liver -- Saturable (mg)
427     RAMet1 = VK1 * CVLiv / (1 + af1*CVLiv)
428     AMet1 = INTEG(RAMet1, 0.0)
429
430 ! Amount in Mammary Tissue (mg)

```

```

431  RAMam = QMam * (CArt - CVMam)
432  AMam = INTEG(RAMam, IAMam)
433  CMam = AMam / VMam
434  CVMam = CMam / PMam
435
436  ! Amount in Placenta (mg)
437  RAPla = (QPla * (CArt - CVPla)) + (PAF * (CFet - CPla))
438  APla = INTEG(RAPla, 0.0)
439  CPla = APla / VPla
440  CVPla = CPla / PPla
441
442  ! Amount in Rapidly Perfused Tissue (mg)
443  RARap = QRap * (CArt - CVRap)
444  ARap = INTEG(RARap, IARap)
445  CRap = ARap / VRap
446  CVRap = CRap / PRap
447
448  !ASKI = AMOUNT NMP IN liquid-exposed SKIN TISSUES (MG) AND DERMAL DOSING (from vapor)
449  ! Liquid exposure when czone = 1, otherwise czone = 0. CI = air concentration
450  czone = pulse(0.0,fullweek,hrsweek)*DZONE
451
452  ! Cardno edit start
453  cczone = czone*pulse(0.0,24,LIQUIDTIME)
454  lcczone=pulse(0.0,24,6)
455
456  ! Cardno edit end
457
458  ! for a 5 day/wk exposure, use fullweek=7*24, hrsweek=5*24 (Dayswk=5)
459  ! for a single day, fullweek=1e16, hrsweek=24 (Dayswk=1)
460
461  RADL = (PVL*SAL/1000.0)*(CSURF - (CSKL/PSKL))*cczone*BRUSH !change to cczone
462  ! Net rate of delivery to "L" skin from liquid, when liquid is there
463  ADLL = integ(RADL, 0.0)
464  RADVL = (PV*SAL/1000.0)*(CI - (CSKL/PSKA))*(1.0-cczone) !change to cczone
465  ! Net rate of delivery to "L" skin from air, when liquid not present
466  ADVL = integ(RADVL, 0.0)
467  ASURF = INTEG(-RADL, DDN) ! Aount in liquid. DDN is the initial amount.
468  VLIQ = (AH20 + ASURF)/DENSITY
469  CSURF = ASURF/VLIQ
470
471  RASKL = QSKL*(CArt - CvSKL) + RADL + RADVL ! Rate of change in "L" skin compartment
472  ASKL = INTEG(RASKL, 0.0) ! Amount in "L" skin
473  CSKL = ASKL/VSKL ! Concentration in "L" skin
474  CvSKL = CSKL/PSKB ! Concentration in venous blood exiting "L" skin
475
476
477  !ASKv = AMOUNT NMP IN vapor-exposed SKIN TISSUES (MG) AND DERMAL DOSING (from vapor);
478  ! "SKv" (vapor-only-exposed) skin compartment. CI = air concentration

```

```

479
480 RADVv = (PV*SAv/1000.0)*(CI*(1.0 - AMASK/SAVC) - (CSKv/PSKA)) ! Net rate of transfer from air to skin
481      ! In above, CI is reduced in proportion to mask fractional coverage (AMASK), so *average*
482      ! concentration of air over exposed skin is reduced from CI by AMASK/SAVC.
483      ! If the concentration inside the mask is 10% of exposure and the surface area fraction of the face
484      ! (covered by the mask) is 'mask' = 0.03, and SAVC is the surface area fraction otherwise exposed,
485      ! then the average concentration of vapor-exposed skin (weighted by surface area) is:
486      ! [(SA fully exposed)*CI + (SA of mask)*10%*CI]/SAVC =
487      ! [(SAVC - mask)*CI + mask*0.1*CI]/SAVC = [1 - 0.9*mask/SAVC]*CI
488      !
489
490      = (1 - AMASK/SAVC)*CI,
491      ! if AMASK = 0.9*mask; i.e., the mask effectively covers 90% of the face, reduces CI by
492 AMASK/SAVC.
493
494      ADVv = INTEG(RADVv,0.0)      !'AMT NMP ABSORBED DERMAL,MG'
495 RASKv = QSKv*(CArt - CvSKv) + RADVv ! Rate of change in "V" skin
496 ASKv = INTEG(RASKv, 0.0)      ! Amount in "V" skin
497 CSKv = ASKv/VSKv      ! Concentration in "V" skin
498 CvSKv = CSKv/PSKb      ! Concentration in venous blood exiting "V" skin
499
500 ! Amount in Slowly Perfused Tissue (mg)
501 RASlw = QSlw * (CArt - CVSlw)
502 ASlw = INTEG(RASlw, IASlw)
503 CSlw = ASlw / VSlw
504 CVSlw = CSlw / PSlw
505
506 ! Amount in Uterus (mg)
507 RAUtr = QUtr * (CArt - CVUtr)
508 AUtr = INTEG(RAUtr, IAUtr)
509 CUtr = AUtr / VUtr
510 CVUtr = CUtr / PUtr
511
512 ! BLOOD VENOUS ARTERIAL (c)
513 CVEN=(QFAT*CVFat + QLIV*CVLiv + QMAM*CVMam + QPLA*CVPla + QRap*CVRap + QSlw*CVSlw &
514      + QUtr*CVUtr + QSKV*CVSKv + QSKL*CVSKL + IV) / QC
515 ivtot=INTEG(IV, 0.0)
516
517 ! Amount in Arterial Blood (mg)
518 RAINH = QAlv*(CI*FRACIN - CAIv)
519 RABld = RAINH + QC*(CVen-CArt) - RAUNP
520 INhaltot = INTEG(RAINH, 0.0)
521 ABld = INTEG(RABld, IAArt)
522 CArt = ABld / VBL
523 CAIv = CArt / PB
524 CAIvPPM = CAIv * 24450.0 / MW
525 AUCCBld = INTEG(CArt, 0.0)
526
527 ! Amount in Urine (mg)

```

```

528 RAUNP = KUMNE*CART                                !FIRST ORDER RATE OF LOSS (URINE
529 AUNP = INTEG(RAUNP,0.0)
530
531 ! ----- HUMAN 5HNMP MODEL -----
532
533 ! Amount in body (mg)
534 RA5H = (RAMet1*STOCH) - RAMetM1 - RAUHP
535 A5H = INTEG(RA5H, 0.0)
536 Cven1 = A5H / VOD5H
537
538 ! Amount Metabolised [in Liver] -- Saturable (mg)
539 RAMetM1 = VK2*Cven1
540 AMetM1 = INTEG(RAMetM1, 0.0)
541
542 ! Amount in Urine (mg)
543 RAUHP = KME*Cven1
544 AUHP = INTEG(RAUHP,0.0)
545
546 ! ----- CHECK MASS BALANCE -----
547 INTOT=INTEG((QAlv*CI*FRACIN), 0.0)
548
549 TDose = INTOT + AO + InitTot+TORAL+ADLL+ADVL+ADV
550 NMPTOT = ABld + AFat + AFet + ALiv + AMam + APla + ARap + ASkl + ASkv + ASlw + AUtr + AExh + AUnp +
551 AMET1
552 MassBal = TDose/(NMPTOT+0.000000000001)
553
554 TERMT(T.GT.TSTOP, 'Simulation Finished')
555
556 END          ! End of Derivative
557
558 TERMINAL
559 DAUCCBld = AUCCBld * 24.0 / TStop
560 DAUCCFet = AUCCFet * 24.0 / TStop
561 END
562
563 END          ! End of Dynamic
564 END          ! End of Program

```

A.2 U.S. EPA NMP PBPK Model Chronic Scenario .m File Modified by Cardno ChemRisk

```

1 tic
2
3 use human_params
4 use human_avg_params
5 BWINIT=74; DAYSWK=5; TSTOP=168; BRUSH=1; VLIQ0=1e6; S3=4.5; P3=4;
6 PVL=4.78e-4; GDSTART = 0; % woman of childbearing age, not pregnant
7 start @nocallback
8 %prepare @clear T CVEN CZONE CI
9
10 %Cardno ChemRisk Edits START ****
11 prepare @clear T CART ADLL CVEN CZONE CCZONE CI
12 CART_ALL = [ ];
13 ADLL_ALL = [ ];
14 fname="NMP_wrkplc_Jan2020_Male_CC.xls"
15 DENSITY = 1020000;
16 %Cardno ChemRisk Edits END ****
17
18 % Start by reading last row # to analyze (A2) and BW (B2) from fname:
19 fst=xlsRead(fname, "chronic exposures data", "A2:B2"); BWINIT=fst(2);
20 % Then set ranges to read data using last row #, and read input data.
21 hrng=ctos(['H3:J',num2str(fst(1))]); dat=xlsRead(fname, "chronic exposures data", hrng);
22 lrng=ctos(['L3:L',num2str(fst(1))]); dconc=xlsRead(fname, "chronic exposures data", lrng);
23 orng=ctos(['O3:O',num2str(fst(1))]); pfg=xlsRead(fname, "chronic exposures data", orng);
24
25 %Cardno ChemRisk Edits START ****
26 krng=ctos(['K3:K',num2str(fst(1))]); tliq=xlsRead(fname, "chronic exposures data", krng);
27 mrng=ctos(['M3:M',num2str(fst(1))]); dpw=xlsRead(fname, "chronic exposures data", mrng);
28 nrng=ctos(['N3:N',num2str(fst(1))]); pvl=xlsRead(fname, "chronic exposures data", nrng);
29 %Cardno ChemRisk Edits END ****
30
31 aglove=890; % cm^2 covered by gloves when worn (when pfg > 1)
32 mask=0.03; % Fraction of skin covered by mask
33 res=[]; % empty results table
34 %CINTC=1
35 salist=[]; % empty array for amount absorbed from vapor through skin
36 for scen=1:length(dconc)
37
38 %Cardno ChemRisk Edits START ****
39 LIQUIDTIME=tliq(scen);
40 if (LIQUIDTIME > 4)
41 LIQUIDTIME = LIQUIDTIME + 0.5 % Add 1/2 hour to day for lunch (code excludes exp). if
42 dermal contact > 4 hours
43 end
44
45 DAYSWK=dpw(scen);
46 %Sets days per week

```

```

47
48 PVL=pvl(scen);
49 %Sets PVL
50
51 %Cardno ChemRisk Edits END ****
52
53 CONCL=dat(scen,1)*DENSITY; SAL=dat(scen,2)/pfg(scen); % SAL = (SA exposed)/(glove PF)
54 CONCMGM=dconc(scen); P2=dat(scen,3); ON3=0; gloves = pfg(scen) > 1; % 1 when gloves on
55 rexp=[scen dat(scen,1) SAL P2 pfg(scen)]; % start row of results
56 if (P2 > 4)
57     ON3 = 1; P3 = P2 - 4; P2 = 4;
58 end
59 rsa=[]; % empty row of results for amount absorbed from vapor through skin
60 for FRACIN=[1 0.1] % "1" is no mask, 100% air conc, 0.1 is air conc reduced 10x by mask
61     AMASK=mask*(1-FRACIN); % zero mask area when no mask, FRACIN=1
62     SAVC=0.25 - (gloves*aglove + (1-gloves)*SAL)/TSA;
63     start @nocallback
64     rexp=[rexp (AUCCBLD*24/TSTOP) max(_cven)];
65     rsa=[rsa,ADV]; % appending to row of results for amount absorbed from vapor through skin
66     if scen==7
67         %plot(_t,_cven,_t_ci*1000,'wrkplot.aps')
68     %plot(_t,_cczone,_t_czone,'wrkplot.aps')
69     end
70 if scen==8
71     %plot(_t,_cven,_t_ci*1000,'wrkplot.aps')
72     %plot(_t,_cczone,_t_czone,'wrkplot.aps')
73     end
74
75 %Cardno ChemRisk Edits START ****
76
77 CART_ALL = [CART_ALL _cart];
78 ADLL_ALL = [ADLL_ALL _adll];
79
80 %Cardno ChemRisk Edits END ****
81
82 end % with/without mask
83 res=[res;rexp] % add results row to results table
84 salist=[salist;rsa]; % appending to results for amount absorbed from vapor through skin
85
86 end % scenario
87 prng=ctos(['p3:x',num2str(fst(1))]);
88 xlsWrite(fname, "chronic exposures data", prng, res);
89
90 %Cardno ChemRisk Edits START ****
91
92 CART_ALL = [_t; CART_ALL]';
93 ADLL_ALL = [_t; ADLL_ALL]';
94

```

```
95  save CART_ALL @file=CART_Male.csv @format=ascii @separator=comma
96  save ADLL_ALL @file=ADLL_Male.csv @format=ascii @separator=comma
97
98  %Cardno ChemRisk Edits END ****
99  toc
```

A.3 U.S. EPA NMP PBPK Model Acute Scenario .m File Modified by Cardno ChemRisk

```

1 tic
2
3 use human_params
4 use human_avg_params
5 BWINIT=74; DAYSWK=5; TSTOP=168; BRUSH=1; VLIQ0=1e6; S3=4.5; P3=4;
6 PVL=4.78e-4; GDSTART = 0; % woman of childbearing age, not pregnant
7 start @nocallback
8 %prepare @clear T CVEN CZONE CI
9
10 %Cardno ChemRisk Edits START ****
11 prepare @clear T CART ADLL CVEN CZONE CCZONE CI
12 CART_ALL = [ ];
13 ADLL_ALL = [ ];
14 fname="NMP_wrkplc_Jan2020_Female_CC.xls"
15 DENSITY = 1020000; % Density in mg/L at skin temperature 40C
16 %Cardno ChemRisk Edits END ****
17
18
19 % Start by reading last row # to analyze (A2) and BW (B2) from fname:
20 fst=xlsRead(fname, "acute exposures data", "A2:B2"); BWINIT=fst(2);
21 % Then set ranges to read data using last row #, and read input data.
22 hrng=ctos(['H3:J',num2str(fst(1))]); dat=xlsRead(fname, "acute exposures data", hrng);
23 lrng=ctos(['L3:L',num2str(fst(1))]); dconc=xlsRead(fname, "acute exposures data", lrng);
24 orng=ctos(['O3:O',num2str(fst(1))]); pfg=xlsRead(fname, "acute exposures data", orng);
25
26 %Cardno ChemRisk Edits START ****
27 krng=ctos(['K3:K',num2str(fst(1))]); tliq=xlsRead(fname, "acute exposures data", krng);
28 mrng=ctos(['M3:M',num2str(fst(1))]); dpw=xlsRead(fname, "acute exposures data", mrng);
29 nrng=ctos(['N3:N',num2str(fst(1))]); pvl=xlsRead(fname, "acute exposures data", nrng);
30 %Cardno ChemRisk Edits END ****
31
32 aglove=890; % cm^2 covered by gloves when worn (when pfg > 1)
33 mask=0.03; % Fraction of skin covered by mask
34 res=[]; % empty results table
35 %CINTC=1
36 salist=[]; % empty array for amount absorbed from vapor through skin
37 for scen=1:length(dconc)
38
39 %Cardno ChemRisk Edits START ****
40 LIQUIDTIME=tliq(scen);
41 if (LIQUIDTIME > 4)
42 LIQUIDTIME = LIQUIDTIME + 0.5 % Add 1/2 hour to day for lunch (code excludes exp. if dermal contact > 4 hours
43 end
44
45 %Sets time for liquid contact
46
47 DAYSWK=dpw(scen);
48 %Sets days per week
49
50 PVL=pvl(scen);

```

```

51  %Sets PVL
52
53  %Cardno ChemRisk Edits END ****
54
55
56  CONCL=dat(scen,1)*DENSITY; SAL=dat(scen,2)/pfg(scen); % SAL = (SA exposed)/(glove PF)
57  CONCMGM=dconc(scen); P2=dat(scen,3); ON3=0; gloves = pfg(scen) > 1; % 1 when gloves on
58  rexp=[scen dat(scen,1) SAL P2 pfg(scen)]; % start row of results
59  if (P2 > 4)
60      ON3 = 1; P3 = P2 - 4; P2 = 4;
61
62  end
63  rsa=[]; % empty row of results for amount absorbed from vapor through skin
64  for FRACIN=[1 0.1] % "1" is no mask, 100% air conc, 0.1 is air conc reduced 10x by mask
65      AMASK=mask*(1-FRACIN); % zero mask area when no mask, FRACIN=1
66      SAVC=0.25 - (gloves*aglove + (1-gloves)*SAL)/TSA;
67      start @nocallback
68      rexp=[rexp (AUCCBLD*24/TSTOP) max(_cven)];
69      rsa=[rsa,ADV]; % appending to row of results for amount absorbed from vapor through skin
70      if scen==7
71          %plot(_t,_cven,_t,_ci*1000,'wrkplot.aps')
72      %plot(_t,_cczone,_t,_czone,'wrkplot.aps')
73
74      end
75
76  if scen==8
77      %plot(_t,_cven,_t,_ci*1000,'wrkplot.aps')
78      %plot(_t,_cczone,_t,_czone,'wrkplot.aps')
79
80      end
81
82  %Cardno ChemRisk Edits START ****
83
84  CART_ALL = [CART_ALL _cart];
85  ADLL_ALL = [ADLL_ALL _adll];
86
87  %Cardno ChemRisk Edits END ****
88
89  end % with/without mask
90  res=[res;rexp] % add results row to results table
91  salist=[salist;rsa]; % appending to results for amount absorbed from vapor through skin
92
93  end % scenario
94  png=ctos(['p3:x',num2str(fst(1))]);
95  xlsWrite(fname, "acute exposures data", png, res);
96
97  %Cardno ChemRisk Edits START ****
98
99  CART_ALL = [_t'; CART_ALL'];
100 ADLL_ALL = [_t'; ADLL_ALL'];
101
102 save CART_ALL @file=CART_Female.csv @format=ascii @separator=comma
103 save ADLL_ALL @file=ADLL_Female.csv @format=ascii @separator=comma

```

104
105
106 **%Cardno ChemRisk Edits END ******
107
108 toc

A.4 Excerpt of U.S. EPA Template Spreadsheet for Chronic Scenarios Modified by Cardno ChemRisk

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X
				Inh. Characterization	hand SA	gloves	Weight frac characterization	Weight Fraction	SA exposed (cm ² - males)	Inh and dermal vapor exposure duration	dermal liquid duration (hr)	Duration- based Air Conc (mg/m ³)	Days per week	PVL (dermal permeability constan used)	Gloves Protection Factor, "1" = none	#	weight fraction	SAL (exposed SA/PF)	Duration	PF	Male worker, AUC, no mask	Male worker, Cmax, no mask	Male worker, AUC, with mask	Male worker, Cmax, mask
1																								
2	30	88																						
3	12 - electronics	central gloves PF 20	Container handling, small containers	50th	central	yes	central	0.6	24.075	12	0.3333333	0.51082	3	0.000478	20	1	0.6	1.20375	12	20	0.09	0.02	0.03	0.01
4		high-end gloves PF 20	Container handling, small containers	95th	high-end	yes	high-end	0.75	80.25	12	1	0.61299	4	0.000478	20	2	0.75	4.0125	12	20	0.22	0.04	0.11	0.04
5		central gloves PF 10	Container handling, small containers	50th	central	yes	central	0.6	24.075	12	0.3333333	0.51082	3	0.000478	10	3	0.6	2.4075	12	10	0.10	0.02	0.03	0.01
6		high-end gloves PF 10	Container handling, small containers	95th	high-end	yes	high-end	0.75	80.25	12	1	0.61299	4	0.000478	10	4	0.75	8.025	12	10	0.30	0.08	0.19	0.07
7		central gloves PF 20	Container handling, drums	50th	central	yes	central	0.5	24.075	12	0.3333333	0.01287	3	0.000478	20	5	0.5	1.20375	12	20	0.01	0.00	0.00	0.00
8		high-end gloves PF 20	Container handling, drums	95th	high-end	yes	high-end	0.75	80.25	12	1	1.55699	4	0.000478	20	6	0.75	4.0125	12	20	0.44	0.05	0.16	0.04
9		central gloves PF 10	Container handling, drums	50th	central	yes	central	0.5	24.075	12	0.3333333	0.01287	3	0.000478	10	7	0.5	2.4075	12	10	0.01	0.01	0.01	0.01
10		high-end gloves PF 10	Container handling, drums	95th	high-end	yes	high-end	0.75	80.25	12	1	1.55699	4	0.000478	10	8	0.75	8.025	12	10	0.52	0.09	0.24	0.08
11		central gloves PF 20	Typical fab worker	50th	central	yes	central	1E-10	1E-10	12	1E-10	0.13894	3	0.000478	20	9	1E-10	5E-12	12	20	0.02	0.00	0.01	0.00
12		high-end gloves PF 20	Typical fab worker	95th	high-end	yes	high-end	1E-10	1E-10	12	1E-10	0.40866	4	0.000478	20	10	1E-10	5E-12	12	20	0.10	0.01	0.02	0.00
13		central gloves PF 10	Typical fab worker	50th	central	yes	central	1E-10	1E-10	12	1E-10	0.13894	3	0.000478	10	11	1E-10	1E-11	12	10	0.02	0.00	0.01	0.00
14		high-end gloves PF 10	Typical fab worker	95th	high-end	yes	high-end	1E-10	1E-10	12	1E-10	0.40866	4	0.000478	10	12	1E-10	1E-11	12	10	0.10	0.01	0.02	0.00
15		central gloves PF 20	Fab worker w/ NMP container changeout	50th	central	yes	central	0.025	24.075	12	0.3333333	0.13894	3	0.000478	20	13	0.025	1.20375	12	20	0.02	0.00	0.01	0.00
16		high-end gloves PF 20	Fab worker w/ NMP container changeout	95th	high-end	yes	high-end	0.05	80.25	12	1	0.40866	4	0.000478	20	14	0.05	4.0125	12	20	0.10	0.01	0.03	0.00
17		central gloves PF 10	Fab worker w/ NMP container changeout	50th	central	yes	central	0.025	24.075	12	0.3333333	0.13894	3	0.000478	10	15	0.025	2.4075	12	10	0.02	0.00	0.01	0.00
18		high-end gloves PF 10	Fab worker w/ NMP container changeout	95th	high-end	yes	high-end	0.05	80.25	12	1	0.40866	4	0.000478	10	16	0.05	8.025	12	10	0.11	0.01	0.03	0.01
19		central gloves PF 20	Maintenance	50th	central	yes	central	0.5	267.5	12	0.3333333	0.02013	3	0.000478	20	17	0.5	13.375	12	20	0.05	0.04	0.04	0.04
20		high-end gloves PF 20	Maintenance	95th	high-end	yes	high-end	1	374.5	12	1	0.69574	4	0.000478	20	18	1	18.725	12	20	0.64	0.24	0.51	0.23
21		central gloves PF 10	Maintenance	50th	central	yes	central	0.5	267.5	12	0.3333333	0.02013	3	0.000478	10	19	0.5	26.75	12	10	0.09	0.08	0.09	0.08
22		high-end gloves PF 10	Maintenance	95th	high-end	yes	high-end	1	374.5	12	1	0.69574	4	0.000478	10	20	1	37.45	12	10	1.12	0.46	0.99	0.46
23		central gloves PF 20	Virgin NMP truck unloading	single value	central	yes	single value	1	80.25	8	0.3333333	4.82219	1	0.000478	20	21	1	4.0125	8	20	0.20	0.14	0.05	0.03
24		high-end gloves PF 20	Virgin NMP truck unloading	single value	high-end	yes	single value	1	267.5	8	1	4.82219	1	0.000478	20	22	1	13.375	8	20	0.27	0.21	0.13	0.17
25		central gloves PF 10	Virgin NMP truck unloading	single value	central	yes	single value	1	80.25	8	0.3333333	4.82219	1	0.000478	10	23	1	8.025	8	10	0.21	0.14	0.06	0.05
26		high-end gloves PF 10	Virgin NMP truck unloading	single value	high-end	yes	single value	1	267.5	8	1	4.82219	1	0.000478	10	24	1	26.75	8	10	0.36	0.37	0.22	0.34
27		central gloves PF 20	Waste truck loading	single value	central	yes	single value	0.92	80.25	8	0.3333333	0.71515	1	0.000478	20	25	0.92	4.0125	8	20	0.04	0.03	0.01	0.02
28		high-end gloves PF 20	Waste truck loading	single value	high-end	yes	single value	0.92	267.5	8	1	0.71515	1	0.000478	20	26	0.92	13.375	8	20	0.11	0.16	0.08	0.15
29		central gloves PF 10	Waste truck loading	single value	central	yes	single value	0.92	80.25	8	0.3333333	0.71515	1	0.000478	10	27	0.92	8.025	8	10	0.04	0.05	0.02	0.05
30		high-end gloves PF 10	Waste truck loading	single value	high-end	yes	single value	0.92	267.5	8	1	0.71515	1	0.000478	10	28	0.92	26.75	8	10	0.18	0.31	0.16	0.30
31																								
32		Key:																						
33		Columns H, I, J, L, and O are primary worker input params																						
34																								
35		Column I has male-specific surf areas																						
36		NOTE: Male body weight value is 88 kg																						

A.5 Excerpt of U.S. EPA Template Spreadsheet for Acute Scenarios Modified by Cardno ChemRisk

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y
				Inh. Characterization	hand SA	gloves	Weight frac characterization	Weight Fraction	SA exposed (cm ² - female)	Inn and dermal vapor exposure duration (hr)	dermal liquid duration (hr)	Duration- based Air Conc (mg/m ³)	Days per week	PVL (dermal permeability constant)	Gloves Protection Factor, "1"	#	weight fraction	SAL (exposed SA/PF)	Duration	PF	Women childbearing age, AUC, no mask	Women childbearing age, Cmax, no mask	Women childbearing age, AUC, with mask	Women childbearing age, Cmax, mask	Acute Moe
1																									
2	34	74																							
3	12 - electronics	central gloves PF 20	Container handling, small container	50th	central	yes	central	0.6	20.025	12	0.33333333	0.510825	3	0.000478	20	1	0.6	1.00125	12	20	0.09	0.02	0.03	0.00	13107
4		high-end gloves PF 20	Container handling, small container	high-end	high-end	yes	high-end	0.75	66.75	12	1	0.61299	4	0.000478	20	2	0.75	3.3375	12	20	0.22	0.04	0.11	0.04	5169
5		central gloves PF 10	Container handling, small container	50th	central	yes	central	0.6	20.025	12	0.33333333	0.510825	3	0.000478	10	3	0.6	2.0025	12	10	0.10	0.02	0.03	0.01	13026
6		high-end gloves PF 10	Container handling, small container	high-end	high-end	yes	high-end	0.75	66.75	12	1	0.61299	4	0.000478	10	4	0.75	6.675	12	10	0.29	0.08	0.18	0.07	2786
7		central gloves PF 20	Container handling, drums	50th	central	yes	central	0.5	20.025	12	0.33333333	0.012873	3	0.000478	20	5	0.5	1.00125	12	20	0.01	0.00	0.00	0.00	60090
8		high-end gloves PF 20	Container handling, drums	high-end	high-end	yes	high-end	0.75	66.75	12	1	1.556994	4	0.000478	20	6	0.75	3.3375	12	20	0.44	0.05	0.16	0.04	4223
9		central gloves PF 10	Container handling, drums	50th	central	yes	central	0.5	20.025	12	0.33333333	0.012873	3	0.000478	10	7	0.5	2.0025	12	10	0.01	0.01	0.01	0.01	30327
10		high-end gloves PF 10	Container handling, drums	high-end	high-end	yes	high-end	0.75	66.75	12	1	1.556994	4	0.000478	10	8	0.75	6.675	12	10	0.51	0.09	0.23	0.08	2486
11		central gloves PF 20	Typical fab worker	50th	central	yes	central	1E-10	1E-10	12	1E-10	0.138944	3	0.000478	20	9	1E-10	5E-12	12	20	0.02	0.00	0.01	0.00	48496
12		high-end gloves PF 20	Typical fab worker	95th	high-end	yes	high-end	1E-10	1E-10	12	1E-10	0.40866	4	0.000478	20	10	1E-10	5E-12	12	20	0.10	0.01	0.02	0.00	16931
13		central gloves PF 10	Typical fab worker	50th	central	yes	central	1E-10	1E-10	12	1E-10	0.138944	3	0.000478	10	11	1E-10	1E-11	12	10	0.02	0.00	0.01	0.00	48496
14		high-end gloves PF 10	Typical fab worker	95th	high-end	yes	high-end	1E-10	1E-10	12	1E-10	0.40866	4	0.000478	10	12	1E-10	1E-11	12	10	0.10	0.01	0.02	0.00	16931
15		central gloves PF 20	Fab worker w/ NMP container change	50th	central	yes	central	0.025	20.025	12	0.33333333	0.138944	3	0.000478	20	13	0.025	1.00125	12	20	0.02	0.00	0.01	0.00	48448
16		high-end gloves PF 20	Fab worker w/ NMP container change	high-end	high-end	yes	high-end	0.05	66.75	12	1	0.40866	4	0.000478	20	14	0.05	3.3375	12	20	0.10	0.01	0.03	0.00	16749
17		central gloves PF 10	Fab worker w/ NMP container change	50th	central	yes	central	0.025	20.025	12	0.33333333	0.138944	3	0.000478	10	15	0.025	2.0025	12	10	0.02	0.00	0.01	0.00	48399
18		high-end gloves PF 10	Fab worker w/ NMP container change	high-end	high-end	yes	high-end	0.05	66.75	12	1	0.40866	4	0.000478	10	16	0.05	6.675	12	10	0.11	0.01	0.03	0.01	16572
19		central gloves PF 20	Maintenance	50th	central	yes	central	0.5	222.5	12	0.33333333	0.020126	3	0.000478	20	17	0.5	11.125	12	20	0.04	0.04	0.04	0.04	5499
20		high-end gloves PF 20	Maintenance	high-end	high-end	yes	high-end	1	311.5	12	1	0.695743	4	0.000478	20	18	1	15.575	12	20	0.61	0.23	0.49	0.22	942
21		central gloves PF 10	Maintenance	50th	central	yes	central	0.5	222.5	12	0.33333333	0.020126	3	0.000478	10	19	0.5	22.25	12	10	0.08	0.08	0.08	0.08	2753
22		high-end gloves PF 10	Maintenance	high-end	high-end	yes	high-end	1	311.5	12	1	0.695743	4	0.000478	10	20	1	31.15	12	10	1.06	0.45	0.94	0.45	478
23		central gloves PF 20	Virgin NMP truck unloading	single value	central	yes	single value	1	66.75	8	0.33333333	4.822186	1	0.000478	20	21	1	3.3375	8	20	0.20	0.14	0.05	0.04	1536
24		high-end gloves PF 20	Virgin NMP truck unloading	single value	high-end	yes	single value	1	222.5	8	1	4.822186	1	0.000478	20	22	1	11.125	8	20	0.27	0.20	0.13	0.17	1067
25		central gloves PF 10	Virgin NMP truck unloading	single value	central	yes	single value	1	66.75	8	0.33333333	4.822186	1	0.000478	10	23	1	6.675	8	10	0.21	0.14	0.06	0.05	1518
26		high-end gloves PF 10	Virgin NMP truck unloading	single value	high-end	yes	single value	1	222.5	8	1	4.822186	1	0.000478	10	24	1	22.25	8	10	0.35	0.36	0.21	0.33	598
27		central gloves PF 20	Waste truck loading	single value	central	yes	single value	0.92	66.75	8	0.33333333	0.715155	1	0.000478	20	25	0.92	3.3375	8	20	0.04	0.02	0.01	0.02	8781
28		high-end gloves PF 20	Waste truck loading	single value	high-end	yes	single value	0.92	222.5	8	1	0.715155	1	0.000478	20	26	0.92	11.125	8	20	0.10	0.15	0.08	0.15	1417
29		central gloves PF 10	Waste truck loading	single value	central	yes	single value	0.92	66.75	8	0.33333333	0.715155	1	0.000478	10	27	0.92	6.675	8	10	0.04	0.05	0.02	0.04	4676
30		high-end gloves PF 10	Waste truck loading	single value	high-end	yes	single value	0.92	222.5	8	1	0.715155	1	0.000478	10	28	0.92	22.25	8	10	0.18	0.30	0.15	0.29	724
31		central gloves PF 20	Plausible maximum acute exposure	single value	central	yes	single value	1	445	12	0.33333333	0.132814	3	0.000478	20	29	1	22.25	12	20	0.18	0.16	0.17	0.16	1372
32		high-end gloves PF 20	Plausible maximum acute exposure	single value	high-end	yes	single value	1	445	12	2	1.178166	4	0.000478	20	30	1	22.25	12	20	1.57	0.52	1.35	0.51	416
33		central gloves PF 10	Plausible maximum acute exposure	single value	central	yes	single value	1	445	12	0.33333333	0.132814	3	0.000478	10	31	1	44.5	12	10	0.34	0.31	0.33	0.31	687
34		high-end gloves PF 10	Plausible maximum acute exposure	single value	high-end	yes	single value	1	445	12	2	1.178166	4	0.000478	10	32	1	44.5	12	10	2.86	1.02	2.65	1.01	211
35																									
36		Key:																							
37		Columns H, I, J, L, and O are primary worker input params																							
38		Column I has FEMALE-specific surf areas																							
39		NOTE: FEMALE body weight value is 74 kg																							
40																									
41		This file is the July 12 outputs from Paul S for FEMALE workers with all PFs for all scenarios except writing only up to PF 5.																							
		acute exposures data																							

Appendix B IH SkinPerm Evaporation Analysis

The current version of IH SkinPerm Version 2.04 was obtained from the AIHA website (<https://www.aiha.org/public-resources/consumer-resources/topics-of-interest/ih-apps-tools>). The model parameter defaults were selected with the exception of the dermal loading parameter which was based on Sahmel et al. (2009). The parameters used in the modeling, including the default parameters for NMP included in the IH SkinPerm model are shown in Table B.1.

B.1 Model Assumptions

Table B-1: IH SkinPerm Parameters for NMP

Parameter	Value	Units	Source
Temperature	25	°C	IH SkinPerm default for NMP
Octanol/water partition coefficient (Log Kow)	-0.38	unitless	IH SkinPerm default for NMP
Water solubility	1000000	mg/L	IH SkinPerm default for NMP
Vapor pressure	46	Pa	IH SkinPerm default for NMP
Molecular weight	99.31	g/mol	IH SkinPerm default for NMP
Density	1030	mg/cm ³	IH SkinPerm default for NMP
Melting point	-24	°C	IH SkinPerm default for NMP
Thickness of stagnant air	1	cm	IH SkinPerm default
Skin surface area	10 100 1000	cm ²	Range of surface areas to test evaporation time
Weight fraction	1	unitless	Maximum from SIA, 2019a
Skin adherence	0.7 - 2.1	mg/cm ²	Sahmel et al. 2009

B.2 Model Results

The IH SkinPerm algorithm was implemented using the parameters shown in Table B.1 to estimate the time to complete evaporation over a range of surface areas. The resulting evaporating times are shown in Table B.2. Evaporation times were found to be 20 minutes for a skin adherence of 0.7 mg/cm² and 60 minutes for a skin adherence of 2.1 mg/cm² for all skin surface areas.

Table B-2: IH SkinPerm Outputs

Surface Area (cm ²)	Skin Adherence (mg/cm ²)	Total Deposition (mg)	Approximate Evaporation Time (min)	Mass Absorbed (mg)	Fraction Absorbed	Mass Evaporated (mg)	Fraction Evaporated
10	0.7	7	20	1.76	25.2%	5.24	74.8%
10	2.1	21	60	4	19.1%	17	80.9%
100	0.7	70	20	17.6	25.20%	52.4	74.8%
100	2.1	210	60	40	19.10%	170	80.9%
1000	0.7	700	20	176	25.20%	524	74.8%
1000	2.1	2100	60	400	19.10%	1700	80.9%

B.3 Example Model Run

Exemplar IH SkinPerm model input and output screens are shown for a skin surface area of 100 cm² and a skin adherence of 0.7 mg/cm² in Figures B.1 and B.2 below.

Figure B-1: IH SkinPerm Model Example Input Screen

AIHA Exposure Assessment Strategies Committee

IH SkinPerm

Data input

- Substance selection**

Choose substance

Database: ☒ SkinPerm ☐ User's

C.A.S. N-methylpyrrolidone (872-50-4)

LogKow at skin pH 5.5: -0.38

add a new substance ...
- Scenario parameters**

☒ Instantaneous deposition ☐ Vapor to skin scenario

☐ Deposition over time ☐ From water solution

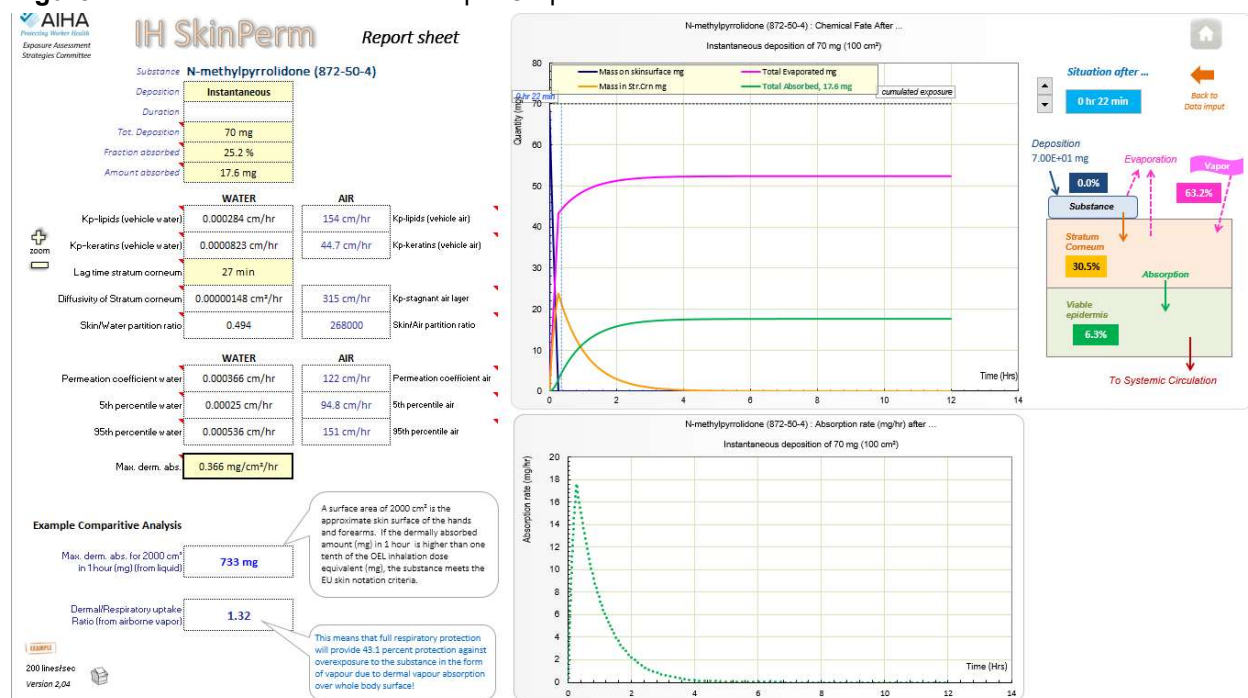
Instantaneous deposition dose	70 mg
Affected skin area	100 cm ²
Maximum skin adherence	0.7 mg/cm ²
Dermal deposition rate	1 mg/cm ² /hr
Air concentration	1 mg/m ³
Thickness of stagnant air	1 cm
Weight fraction	1.00E+00
Concentration in water	0.00162 mg/L
Thickness of water layer	1000 cm
- Timing parameters**

Start deposition	0 hr
Duration of deposition	0 hr
End time observation	12 hr
- Report parameters**

Calculation intervals/hour	10000
Report intervals/hour	200
- START** **RESET**

Version 2,04

Figure B-2: IH SkinPerm Model Example Output Screen



About Cardno

Cardno is an ASX-200 professional infrastructure and environmental services company, with expertise in the development and improvement of physical and social infrastructure for communities around the world. Cardno's team includes leading professionals who plan, design, manage, and deliver sustainable projects and community programs. Cardno is an international company listed on the Australian Securities Exchange [ASX:CDD].

Cardno Zero Harm

Cardno
ZERO
HARM
EVERY JOB. EVERY DAY.

At Cardno, our primary concern is to develop and maintain safe and healthy conditions for anyone involved at our project worksites. We require full compliance with our Health and Safety Policy Manual and established work procedures and expect the same protocol from our subcontractors. We are committed to achieving our Zero Harm goal by continually improving our safety systems, education, and vigilance at the workplace and in the field. Safety is a Cardno core value and through strong leadership and active employee participation, we seek to implement and reinforce these leading actions on every job, every day.

Attachment B: Example Personal Protective Equipment Training Programs

Donning and Doffing Gloves

Glove inspection



Do a visual check of the gloves.



Roll the glove to trap air and check for leaks.

Putting gloves on



Place the gloves on your hands and roll the cuff about one inch.



If apron or sleeves are required, place sleeve over glove cuff.*

** For limited exceptions approved by ESH, check hazard assessment and procedures.*

Donning and Doffing Gloves

Glove removal



How to remove gloves is very important. Roll the first glove half way down.



Use the inside of first glove to help remove the second glove.

Glove disposal



Dispose of contaminated gloves in proper containers. Always read the label prior to adding contaminated items to a waste container.



– PPE: Chemically-Resistant Gloves

Learning Item: 336001

PPE: Chemically-Resistant Gloves



Goal

This training covers chemically-resistant gloves. The purpose of this eLearning course is to inform workers of chemically-resistant glove requirements and limitations and how to properly wear and maintain them.

Objectives

At the conclusion of this training workers will be able to:

- Demonstrate proper donning, doffing, adjusting, and wearing of the required Personal Protective Equipment (PPE).
- Describe the limitations (durability, useful life, incompatibilities) of the specified PPE materials.
- Describe proper care, maintenance, and disposal of the applicable PPE items.

- PPE: Chemically-Resistant Gloves



Learning Completion

Prior to wearing Chemically-Resistant Glove PPE at _____, workers must complete the following through the SF Learning system:

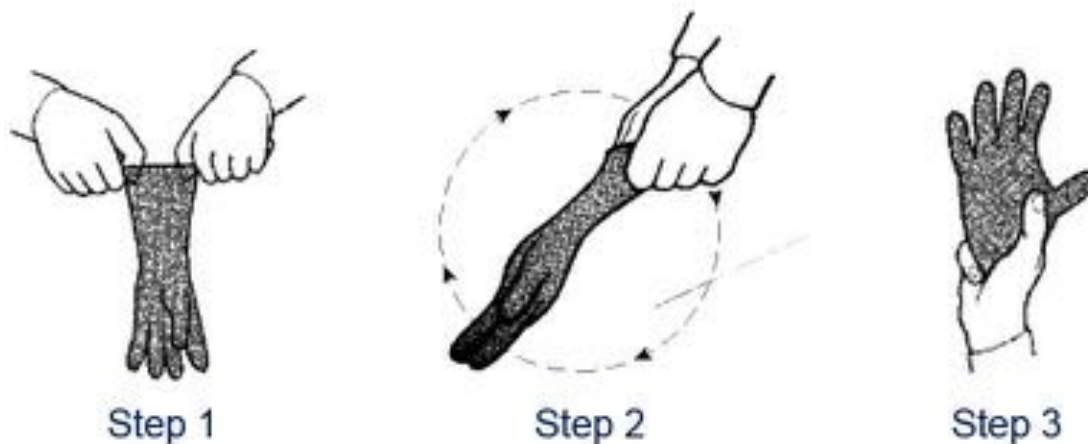
1. **E_LRN 336001**: Review this presentation to gain a full understanding of the PPE-specific training content, and complete the associated quiz (biennial requirement).
 2. **CERT 79461**: Perform a 'hands-on' demonstration of donning, doffing, and wearing of the PPE item(s) under the direction of their supervisor or a qualified designee (one-time certification).
- Both requirements (eLearning, certification) can be found as individual learning items located on the worker's SF Learning plan.

- PPE: Chemically-Resistant Gloves



■ Chemically-Resistant Gloves: *Donning, doffing, adjusting, and wearing*

- Select a glove size that fits snugly and comfortably without excess amounts of loose or bunched-up material that could interfere with work activities.
- Check the gloves for pin-hole leaks (see below) and other defects, such as cracks, tears, material thinness, etc. before donning.



- PPE: Chemically-Resistant Gloves



■ Chemically-Resistant Gloves: *Donning, doffing, adjusting, and wearing*

- Wear two pair of North natural rubber “Acid” gloves when contact with corrosive liquid is likely.
- Ensure that gloves cover the entire hand surface and are pulled up over the wrist/lower arm.
- Remove by carefully turning the glove inside out from the cuff to the fingers without touching the outer surface of the protective glove.



Silver Shield Glove



North 'Acid' Glove



Nitrile Glove

- PPE: Chemically-Resistant Gloves



■ Chemically-Resistant Gloves: *Limitations*

- Chemically-resistant gloves are intended for one single use prior to disposal.
- Wear to protect against small, incidental splashes or spills; they are typically not intended for continuous chemical contact. Promptly remove for appropriate disposal upon unintended contact with chemical materials.
- Gloves are not very durable, and they can be easily punctured or torn, particularly during physical work with hand tools. Check for damage or weakness regularly during work, and immediately remove and replace damaged gloves.
- The level of chemical resistance of the glove material will vary depending on the identity of the contacted chemical. The glove material allows most of the contacted liquid to run off, but some chemicals may penetrate through the material over time.

- PPE: Chemically-Resistant Gloves



■ Chemically-Resistant Gloves: *Care, maintenance, and disposal*

- Store in a designated climate-controlled location and in a manner that will not damage the structural integrity of the chemically-resistant material.
- Do not attempt to repair or tape damaged gloves; properly dispose of the damaged gloves, and replace immediately with a new pair.
- Dispose of potentially contaminated gloves according to the specific area requirements (place in the area designated waste container). Contact the Environmental Compliance Department for assistance, if needed.



- PPE: Chemically-Resistant Gloves



Next steps

1. Please return to your SF Learning plan to complete the quiz.
2. Refer to your area procedures to determine what chemically-resistant glove PPE is required and when it is necessary for specific tasks. Work with your area to ensure you are aware of the location of the PPE you will need to wear.
3. Contact your supervisor to be certified on this PPE. You will perform a 'hands-on' demonstration of donning, doffing, and wearing of the PPE item(s). Your supervisor may use the [Demonstration Checklist](#) as a guideline for performing the certification process and to sign you off in your SF Learning plan. You may wish to preview the Demonstration Checklist before you ask to be certified to familiarize yourself with the steps you will be asked to perform.
 - *Note: A supervisor may select a qualified designee to observe the demonstration for certification purposes (the supervisor would then sign-off on the certification in SF Learning).*

Refer to the site [PPE Catalog](#) for listings of approved PPE items, SAP part numbers, images, vendor links, and other additional PPE information.

Email [redacted] or directly contact any member of the [redacted] Safety Department if you have questions or comments.

Document Control Information

ECN Facility:		ECN Area:	
Owner(s):	Safety	Target Audience:	workers with future certifications in LI #79461
Document Type:	Training	DOC ID#:	H7HV5MEZRJEZ-401591482-287
Review Schedule:	Biennial	Last Modified:	10/27/2017
<u>ECN History</u>		<u>Submit an ECN</u>	

- **Approval:** BOIFAC_SAFETY_PPE_APPR
- **Notification:** BOIFAC_SAFETY_TEAM
- **Final Viewer Access:**
 - ALL_ _EMPLOYEE_WORKERS
 - ALL_ _CONTRACTOR_WORKERS
- **Retention:** MFG – Controlled Document (10 years)

October 30, 2017

– Personal Protective Equipment (PPE) Program

ECN Facility: FACILITIES -

ECN Area:

Owner(s): Safety Department

Target Audience: Safety Workers, Area Supervisors, Area Trainers

Document Type: Program

DOC ID: H7HV5MEZRJEZ-401591482-139

Review Schedule: Biennial

Last Modified: 3/26/2018

[ECN History](#)

[Submit an ECN](#)

1.0 Purpose

- To ensure workers have and properly use the appropriate personal protective equipment (PPE) to protect them from the hazards that they may encounter in the workplace.
- To ensure meet the requirements set forth in the OSHA Personal Protective Equipment standard ([29 CFR 1910.132](#)).

2.0 Scope

- **Site(s) impacted:** Sites
- **Target user audience:** Safety Department employees, area supervisors/hosts.
- Non-employees (e.g. contractors, vendors, equipment representatives, etc.) must also comply with the requirements of this program through the direction and supervision of their hosts.
 - Contractors creating their own hazard based on the specialized work they are performing will be responsible for both the proper selection/use of PPE for their own workers as well as communicating this information to any other affected workers.
 - If a contractor's work involves potential exposure to hazardous materials or processes, will inform them of the hazards and recommend appropriate PPE, as needed.

3.0 Safety

3.1 Job Hazard Analysis

This document was evaluated for potential job hazards. This procedure includes no recognized risks and a Job Hazard Analysis (JHA) record is not required. If changes are required to this procedure, those changes must be evaluated for potential job hazards. For additional JHA information, refer to the JHA site, web alias [JHA](#).

4.0 Definitions and Acronyms

- **OSHA:** Occupational Safety and Health Administration
- **PPE:** Personal Protective Equipment

5.0 Roles and Responsibilities

Title or Department	Role or Responsibility
Safety Department employees	<ul style="list-style-type: none">• Assist areas or departments complete their workplace hazard assessments (i.e., job hazard analyses), if needed• Assist area supervisors/hosts with PPE selection & training, as necessary
Area supervisors/hosts	<ul style="list-style-type: none">• Ensure that workers demonstrate an understanding of the PPE training and the ability to use PPE properly• Select and have each affected worker use the types of PPE that will protect the affected worker from identified area hazards• Contact the Safety Department for assistance with PPE selection and training, if necessary• Communicate selection decisions to affected workers (i.e., direct communication, written procedures, JHAs, etc.)• Ensure that direct reports accomplish and maintain their PPE training requirements/certifications, as necessary for the area or tasks to be performed and as required in SF Learning
Safety Department Industrial Hygienist(s)	<ul style="list-style-type: none">• Evaluate PPE to ensure safe design and construction for the work to be performed
workers	<ul style="list-style-type: none">• Wear the PPE as required by area procedures/JHAs/work plans to protect against identified hazards

6.0 Personal Protective Equipment (PPE) Program

6.1 OSHA Requirements

This program addresses the federal legal requirements in the Occupational Safety and Health Administration's (OSHA) Personal Protective Equipment standard, [29 CFR 1910.132](#), and other information necessary for to meet these obligations¹.

6.1.1 To comply with the OSHA PPE standard shall:

- Assess the workplace to determine if hazards are present,
- Select and have each affected worker use PPE that will protect them from the hazards, and
- Train workers on the proper use of PPE.

6.2 Workplace Hazard Assessment & PPE Selection

- 6.2.1 will conduct a hazard assessment of the work areas/tasks to determine if hazards are present, or are likely to be present, which warrant the use of PPE.
- 6.2.2 As part of the site risk assessment process employees assess the hazards of work areas and tasks to be performed.
- 6.2.3 must verify that the required workplace hazard assessment has been performed through a written certification.
- 6.2.4 Hazard assessments are formally documented on job hazard analysis (JHA) forms that also include and/or comply with the following:
- The workplace/location that was evaluated—*completed JHAs identify the workplace location that was evaluated.*
 - The person certifying that the evaluation has been performed—*completed JHAs list the name of the person that performed the analysis.*
 - The date of the hazard assessment—*completed JHAs include the date that the evaluation was completed.*
 - Identification of the document as a certification of hazard assessment—*completed JHAs shall serve as written certification(s) of hazard assessment.*
- 6.2.5 If workplace hazards are present, or likely to be present, the department or area supervision (with the assistance of a Safety employee, if necessary) shall:
- Select, and have each affected worker use, the types of PPE that will protect the affected worker from the hazards identified in the workplace hazard assessment;
 - Communicate selection decisions to each affected worker and
 - Select PPE that will properly fit each affected worker.
- 6.2.6 All PPE will be of safe design and construction for the work to be performed.
- Only PPE that has been previously approved by the Safety Department should be used (see [PPE Catalog](#)).
 - Defective or damaged PPE may not be used.
- 6.2.7 Workers must wear the selected PPE as required by their supervisors, area procedures, or JHAs to protect against identified hazards in the workplace.

6.3 Training

- 6.3.1 The supervisor (with assistance from Safety, if necessary) will provide training to workers who are required to wear and use PPE. Each worker shall be trained to know at least the following:
- What PPE is required and when it is necessary;
 - How to properly don, doff, adjust, and wear PPE;
 - The limitations (e.g. durability, useful life, incompatibilities, etc.) of the PPE; and
 - The proper care, maintenance, and disposal of the PPE.
- Note:** See individual PPE documents (listed below) for more detailed training reference material.

- 6.3.2 If _____ provides the PPE to contractors, vendors, equipment representatives, etc., the Micron host or designee (with assistance from Safety, if necessary) will also provide the training on its proper use.
- 6.3.3 Trained workers will demonstrate both an understanding of this training and the ability to use PPE properly before being allowed to perform work requiring the use of PPE.
- Area supervisors/hosts (with assistance from Safety, if necessary) will verify that each affected worker has received and understood the required training.
 - PPE certifications in SF Learning must contain at least the following:
 1. Names of each employee trained,
 2. Date(s) of the training, and
 3. Subject(s) of the certification.
 - The following PPE training items are currently available through SF Learning:
 1. Chemically-resistant clothing:
 - [Chemically-Resistant Clothing Training Presentation](#)
 - [Chemically-Resistant Clothing Demonstration Checklist](#)
 - SAFETY - PPE: Chemically-Resistant Clothing (eLearning) (E_LRN 333009)
 - SAFETY - PPE: Chemically-Resistant Clothing (Certification) (CERT 79513)
 2. Chemically-resistant gloves:
 - [Chemically-Resistant Gloves Training Presentation](#)
 - [Chemically-Resistant Gloves Demonstration Checklist](#)
 - SAFETY - PPE: Chemically-Resistant Gloves (eLearning) (E_LRN 336001)
 - SAFETY - PPE: Chemically-Resistant Gloves (Certification) (CERT 79461)
 3. Encapsulating (Level A) Suit:
 - [Encapsulating \(Level A\) Suit Training Presentation](#)
 - [Encapsulating \(Level A\) Suit Demonstration Checklist](#)
 - SAFETY - PPE: Encapsulating (Level A) Suit (eLearning) E_LRN 336003)
 - SAFETY - PPE: Encapsulating (Level A) Suit (Certification) (CERT 79549)
 4. Eye and Face Protection:
 - [Eye & Face Protection Training Presentation](#)
 - [Eye & Face Protection Demonstration Checklist](#)
 - SAFETY - PPE: Eye & Face Protection (eLearning) (E_LRN 333006)
 - SAFETY - PPE: Eye & Face Protection (Certification) (CERT 79469)

5. Work, Thermal, and Cut-Resistant Gloves:

- [Work, Thermal, & Cut-Resistant Gloves Training Presentation](#)
- [Work, Thermal, & Cut-Resistant Gloves Demonstration Checklist](#)
- SAFETY - PPE: Work, Thermal, and Cut-Resistant Gloves (eLearning) (E_LRN 333010)
- SAFETY - PPE: Work, Thermal, and Cut-Resistant Gloves (Certification) (CERT 79546)

6. Head Protection:

- [Head Protection Training Presentation](#)
- [Head Protection Demonstration Checklist](#)
- SAFETY - PPE: Head Protection (eLearning) (E_LRN 333008)
- SAFETY - PPE: Head Protection (Certification) (CERT 336006)

7. Disilane Protective Gear:

- [Disilane Protective Gear Training Presentation](#)
- [Disilane Protective Gear Demonstration Checklist](#)
- SAFETY - PPE: Disilane Protective Gear (eLearning) (E_LRN 336004)
- SAFETY - PPE: Disilane Protective Gear (Certification) (CERT 156101)

8. Flame-Resistant Clothing:

- [Flame-Resistant Clothing Training Presentation](#)
- [Flame-Resistant Clothing Demonstration Checklist](#)
- SAFETY - PPE: Flame-Resistant Clothing (eLearning) (E_LRN 333007)
- SAFETY - PPE: Flame-Resistant Clothing (Certification) (CERT 107409)

6.3.4 Retraining of workers may be necessary under certain circumstances including:

- Changes in the workplace render previous training obsolete;
- Changes in the types of PPE required to be used due to area hazards render previous training obsolete; and
- Inadequacies in an affected employee's knowledge or use of assigned PPE indicate that the employee has not retained the requisite understanding or skill.

7.0 Document Control

- **Approval:** _SAFETY_MANAGER
 - **Notification:** _SAFETY_TEAM
 - **Final Viewer Access:** ALL_ _EMPLOYEE_WORKERS;
ALL_ _CONTRACTOR_WOF)
 - **Retention:** MFG - Controlled Document (10 years)
-

8.0 Quality Management

- The PPE Program shall be reviewed at least biennially by pertinent EHS management (or designees) and updated as necessary to improve the system or meet the requirements of the most current federal and Micron standard(s).
- Periodic reviews and updates shall be evidenced through the periodic document review (PDR) process and any associated revision comments or document changes.
- Document updates that include content changes shall be routed (e.g., email notification, EDM Inbox notification, etc.) by the Safety Department to impacted workers for approval/review.

9.0 Related/Associated Documents and References

- [Personal Protective Equipment \(29 CFR 1910.132\)](#)
- [Workplace Hazard Assessment & PPE Selection](#)
- [Certification of Workplace Hazard Assessment](#)
- [MTI PPE Catalog](#)
- [Eye and Face Protection \(29 CFR 1910.133\)](#)
- [Head Protection \(29 CFR 1910.135\)](#)
- [Foot Protection \(29 CFR 1910.136\)](#)
- [Hand Protection \(29 CFR 1910.138\)](#)
- [Respiratory Protection \(29 CFR 1910.134\)](#)
- [Electrical Protective Devices \(29 CFR 1910.138\)](#)

¹ Sections 6.2 and 6.3 of this Program apply only to (1) Eye and Face Protection ([29 CFR 1910.133](#)), (2) Head Protection ([29 CFR 1910.135](#)), (3) Foot Protection ([29 CFR 1910.136](#)), and (4) Hand Protection ([29 CFR 1910.138](#)). Workplace Hazard Assessment and Training requirements for Respiratory Protection ([29 CFR 1910.134](#)) and Electrical Protective Devices ([29 CFR 1910.138](#)) are addressed separately in other programs or procedures (e.g. [Respiratory Protection Program](#)).

PPE DEMONSTRATION CHECKLIST

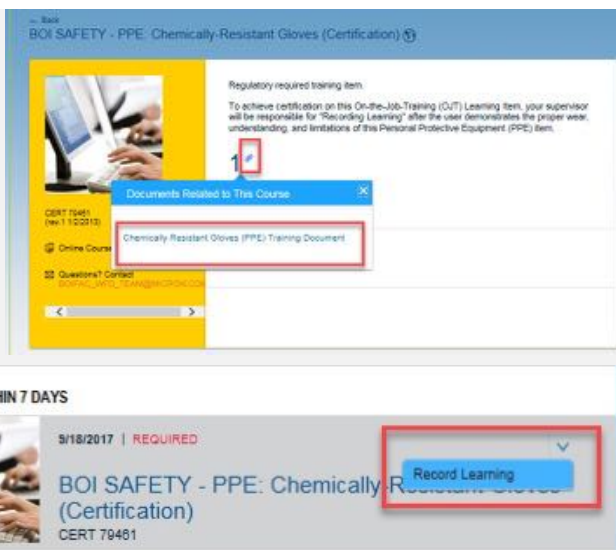
BOI SAFETY - PPE: Chemically-Resistant Gloves (CERT 79461)

As part of the Personal Protective Equipment standard, OSHA requires that affected workers *demonstrate the ability to use PPE properly*. The expectation to satisfy this requirement is to have the certifying worker perform a hands-on demonstration of the donning, wearing, and proper removal of the PPE item(s) under the direction of their supervisor or a qualified designee selected by the supervisor.

This demonstration checklist may be used as a guidance document by the supervisor or qualified designee as the certifying worker demonstrates their ability to properly use the PPE items.

Supervisor:

1. To sign off this certification, launch the team member's SF Learning Plan and select the PPE Certification Learning Item. Select the paper clip icon to view the elearning Training Presentation for reference, if needed.
2. You or your designee will observe the team member perform the actions on the checklist below. If tasks are completed successfully, sign the team member off by selecting **Record Learning**.



Chemically-resistant gloves (e.g. 'Acid' gloves, nitrile gloves, latex gloves, Silver Shield gloves, etc.):

1. Put on the PPE item -
 - ☐ Select a glove size that fits snugly and comfortably without excess amounts of loose or bunched up material that could interfere with work activities.
 - ☐ Check the gloves for pin-hole leaks (see Figure One next page) and other defects, such as cracks, tears, material thinness, etc. before donning.
 - ☐ Ensure that gloves cover the entire hand surface and are pulled up over the wrist/lower arm.
2. Properly remove the PPE item -
 - ☐ Remove by carefully turning the glove inside out from the cuff to the fingers without touching the outer surface of the protective glove.

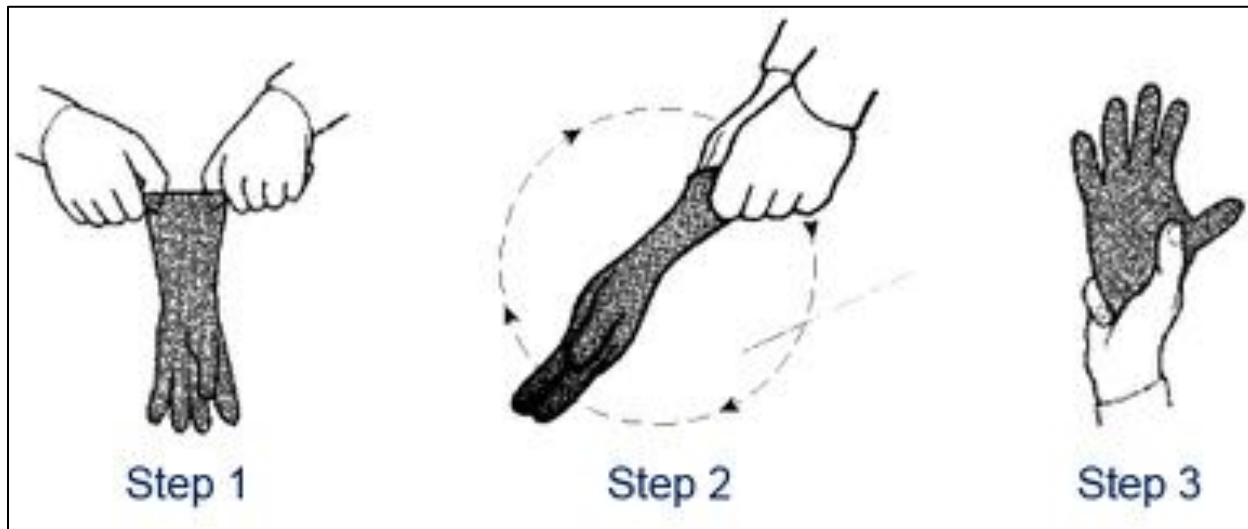




Figure One

i. Donning Chemical Resistant PPE

Step	Action	Note/Results
1.	<p>Don dry, clean chemical-resistant gloves over.</p> 	<p>Place a 2 to 3 inch cuff in the glove to catch any drips which may run down the gloves.</p>
2.	<p>Don the chemical resistant gown by placing neck strap over the head and placing arms into the sleeves.</p> 	<p>Place the gown sleeve over or under the glove cuff (either is acceptable) such that chemicals can not directly contact the skin in the event of a splash or liquids being on the glove. Tighten the sleeve of the gown over the glove using draw string and tie off (if applicable). Taping once around the wrist with clean room tape is recommended when reaching or when the sleeve is not snug around the glove cuff. Create a 2" tab for easy removal by folding the tape back onto itself.</p>
3.	<p>Put on protective eyewear, note splash resistant goggles required when handling corrosives.</p> <p>When wearing Dryden helmet: attach Dryden helmet face shield.</p>	<p>Ensure that the fit is comfortable and is not too tight or too loose. Move head side to side and up and down to ensure that the goggles will not slip during usage.</p> <p>Keep safety glasses on; Chemical goggles are not required when wearing helmet.</p>
4.	<p>Don the face shield.</p>	<p>The face shield must be worn down over the face when ever there is the potential for splash to the face area i.e. pouring chemicals, wiping up freestanding liquids, etc.</p>

Personal Protective Equipment (PPE) for Chemical Handling

Course #



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Course Introduction

The goal of this course is to teach you how to properly use Personal Protective Equipment (PPE) to prevent chemical exposure and how to transport/store hazardous chemicals.

The target audience of this course is all employees that perform chemical handling tasks and includes manufacturing technicians, process and equipment engineers, facilities technicians, and lab workers.



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Course Objectives

At the end of this class, you will know how to:

- Properly use your PPE so that it provides adequate protection against exposure to solid or liquid chemicals.
- Properly inspect, don, decontaminate, doff and dispose of your PPE.
- Properly transport, pour, and store chemicals.

This course does not cover respiratory protection or PPE for Lasers. Respiratory protection equipment and PPE for non-chemical hazards is covered in other safety courses.

If your job scope requires use of a respirator and/or non-chemical hazard PPE, additional training will be required.

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Course Outline

This course consists of four modules and a final assessment

- Intro to PPE
- PPE Selection
- Donning and Doffing PPE
- Chemical Handling Safety
- Final Assessment



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Module 1: PPE Overview

- Personal Protective Equipment (PPE) is used to provide a barrier between the worker and the hazard.
- PPE is effective against potential chemical exposures given that it is appropriately selected for the chemical hazard, used properly and maintained.
- PPE should be used in conjunction with proper work practices, engineering controls and hazard awareness training.
- **PPE does not eliminate the hazard!**

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Module 1: PPE Limitations

Be cautious of these limitations while using PPE:

- If you do not use the proper PPE or use it correctly, it may not provide protection and may result in a harmful chemical exposure.
- PPE may be uncomfortable to wear.
- PPE can reduce your visibility and dexterity.
- PPE can be physiologically stressful (e.g. heat stress).
- Work time may be limited by effectiveness of PPE against a given hazard.
- PPE needs to be maintained properly to work effectively.



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Module 1: PPE Assessments

EHS PPE assessments take into account the following factors to ensure the proper PPE is selected for the task:

- Nature of the hazards - corrosive, irritant, toxicity of material, airborne contaminants.
- Task being performed - duration of the task and potential for chemical contact.
- PPE materials of construction - chemical protection ratings, compatibility, permeation rates, durability.
- Needs of the employee or task requirements- manual dexterity, heat stress, kneeling, crawling or reaching.

All PPE utilized must be reviewed and approved by EHS.

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Module 2: Chemical PPE Selection

Personal protective equipment consists of several parts. The chemical PPE used at Intel includes:

- Protective Face/Eyewear
- Hand protection
- Body protection
- Foot protection
- Flame retardant PPE for pyrophoric materials



Every chemical handling task should be analyzed for the appropriate PPE. Let's look at each part of PPE in more detail.

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Module 2: Chemical Protective Eyewear

Eye protection should be worn to protect the eyes from injury by chemical contact.

Examples of protective eyewear include:

- Safety glasses with side shields.
- Chemical goggles.
- One-piece goggle/face shield combinations.
- A Powered Air Purifying Respirator with built in face shield



Eyewear must be approved for the intended use or application.

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Module 2: Safety Glass Requirements

Safety glasses must have the following characteristics:

- Side shields.
- Impact resistant lenses.
- Frames which help prevent lenses from being pushed into eyes.
- The manufacturer's logo etched into each lens.
- The ANSI Z87/ EN166 marking stamped into the temple of the frames.



Safety Glasses

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Module 2: Chemical Goggles Requirements

Chemical goggles must have the following characteristics:

- Void of vents with the exception of special venting configurations to prevent splashes from reaching the eyes.
- The ANSI Z87/ EN166 marking stamped into the temple of the frames.



Chemical Goggles

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Module 2: Face Shield Requirements

- Face shields must be worn with safety glasses for impact protection from flying debris/objects
- Face shields must be worn with chemical goggles for splash protection against corrosive chemicals.
- The ANSI Z87/ EN166 marking stamped into the temple of the frames.
- Face shields should extend below the user's chin.



Face Shields

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Module 2: Limitations of Eyewear

Chemical protective eyewear requirements are based on the task and determined by EHS.

- A chemical goggle/face shield combination is **required** if the task could potentially result in a corrosive chemical splash to the eyes and face.
- A chemical goggle/face shield combination is **recommended** if the task could potentially result in an irritant chemical splash to the eyes and face.

Be sure to wear the appropriate eyewear per specific task requirement and recognize the following limitations:



- Safety glasses are not a substitute for chemical goggles.
- Face shields do not provide eye protection.
- Face shields do not protect in the 'UP' position.

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Module 2: Chemical Hand Protection

Chemical resistant gloves are required when handling certain chemical materials.

Use of chemical hand protection does not waive the general restriction regarding immersion activities.

Do **not** immerse your hands within chemicals. Handling tools/jigs may be required to prevent gloved hands from being immersed in chemicals.



Chemical Resistant Gloves

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Module 2: Hand Protection Limitations

Limitations of chemical hand protection include:

- Due to the variable chemical resistance of gloves to specific chemicals, task durations may require adjustment to prevent breakthrough and degradation of glove material.
- Reduced dexterity.
- Do not touch common work surfaces such as doors, handles and phones. When wearing chemical hand protection, assume that the gloves have contacted chemicals.
- Do not touch your skin or clothing while wearing PPE.



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Module 2: Whole Body Protective Wear

Whole body protection should be worn when the work task could result in chemical splashes over the entire body or when toxic chemicals can potentially contaminate work clothing.

Examples of whole body protection include:

- Aprons
- Coveralls
- Full-body suits
- Chemical resistant suits



Corrosive Gear - face shield, chemical goggles, chemical resistant gloves, chemical apron

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Module 2: Disposable & Standard Clothing

Disposable clothing may be required when there is potential for contact with hazardous materials in a dry/dust form such as arsenic, lead and/or asbestos.

Standard work clothing (i.e. normal street clothing) is acceptable when working with low toxicity materials such as oils, greases and/or non toxic dusts.

Note: Clean room gowns (bunny suits) do not provide skin protection against corrosive liquids and/or hazardous materials



Disposable Tyvek Clothing

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Module 2: Chemical Protective Footwear

Chemical protective footwear should be worn when the work task has the potential to result in chemical exposure of the feet. The type of footwear required is dependent on the likelihood of a chemical splash.

Types of chemical resistant footwear:

- Chemical resistant boots that have met the NFPA 1991 testing criteria or are stamped with the ISO EN 20345 marking.
- Chemical resistant disposable booties.
- Non-porous, leather-type footwear.



Chemical Boots



Leather Footwear

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Module 2: Note on PPE Selection

ALWAYS refer to the operation and preventive maintenance specifications or documented procedures for the appropriate PPE requirements.

If your specification does not clearly define the appropriate PPE for your task, **STOP** what you are doing and contact your supervisor or site EHS.



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Module 3: Donning and Doffing PPE

Proper donning and doffing is critical to the safe use of PPE. Steps in the process are dependent on the chemical handling task being performed (e.g. potential for chemical contact) and may vary by local site procedures. The donning/doffing instructions detailed in Module 3 should be followed unless alternative donning/doffing procedures have been reviewed and approved by your site EHS.

Refer to your written specs or a documented procedure for details on which PPE is needed for a particular task.

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Module 3: Donning PPE Steps Example

An example of the donning process for handling chemical corrosive liquids is to:

1. Inspect the PPE
2. Don the chemical resistant **gloves**
3. Don the chemical resistant **apron**
4. Don the chemical resistant **goggles**
5. Don the **face shield**



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Module 3: Inspect the Eyewear & Face Shield

ALWAYS inspect your PPE before donning it.

- Ensure that the safety glasses side shields are in place.
- Check your chemical goggles and your face shield for cracks, scratches, and pits.
- Determine if damaged eyewear can be repaired and disposition as appropriate for repair. Non-repairable items should be discarded.
- Follow your Site's procedure for disposing of damaged eyewear.



Inspect Face Shield



Inspect Goggles

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Module 3: Inspect the Chemical Gloves

Check your gloves for discoloration, cuts, tears, holes and changes in thickness of the material. If a leak or suspected manufacturing defect is detected on a new glove, report the issue to your supervisor and commodities buyer as you may have identified a quality assurance problem. Save the defective item and associated packaging to aid in the identification of manufacturing defects.

Check your gloves for pin hole leaks.

1. Inflate the glove - roll the cuff to inflate the glove or use an Oil Free Air or N₂ gun to inflate it.
2. Squeeze the glove to ensure fingers are filled with air.
3. Hold the inflated glove close to exposed skin so you can detect any pin hole leaks.




Check glove for pin hole leaks

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Video Inspecting PPE

Click  to view the video. Proceed to the next page after the video ends.



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Module 3: Donning the Gloves

Don your PPE after you've inspected it.

- Don dry, clean, chemically resistant gloves and place a 2 to 3 inch cuff on the glove to catch any drips which may run down the gloves.



2" to 3" cuff on glove

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Module 3: Donning the Gown

Don your chemical resistant gown.

- Place your arms in the sleeves.
- Ask your buddy to fasten the two sets of ties on the back chemical apron.
- Place the sleeve of the gown over the glove cuff to prevent chemical exposure to the skin.
- For additional protection from liquid intrusion under the gown cuff, it is acceptable to wrap chemical compatible tape around the gown's elastic sleeve and the chemical protective glove (see video instruction).



Ensure the gown's elastic sleeve is over the glove cuff

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Module 3: Donning the Goggles

Don your chemical goggles.

- Tighten the chemical goggle strap.
- Ensure that the fit is comfortable and is not too tight or too loose.
- Move head side to side and up and down to ensure that the goggles will not slip during usage.

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Module 3: Donning the Face Shield

Don the face shield over the chemical goggles or safety glasses and tighten the brow band to ensure that the face shield stays in place while working.


- A chemical goggle/face shield combination is **required** if the task could potentially result in a chemical splash of a corrosive material to the eyes and face.
- A chemical goggle/face shield combination is **recommended** if the task could potentially result in an strong irritant chemical splash to the eyes and face.







Corrosive Chemical PPE


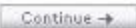

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Video Donning PPE

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Video

Video

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Module 3: Doffing the Face Shield & Goggles

PPE can be safely doffed after the task has been completed.
Doff your PPE in the reverse order that you put it on – **FIRST ON LAST OFF!**

- Always decontaminate (wipe off or rinse) your PPE to remove any chemical liquids or residues. This prevents accidental contact with chemicals while doffing your PPE.
- **Doff your face shield.**
 - Take off your face shield and wipe it down to remove contamination. DI water or 6% IPA wipes can be used to clean the face shield.
 - For corrosive chemicals pH indicator paper and DI water can be used to spot check the pH of your face shield.
 - Return your face shield to its designated storage area.
- **Doff your goggles.**

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Module 3: Doffing the Gown

Remove your gown by drawing your arms out. Take care to not touch the outside of the gown.

Properly dispose of your gown after use.

- Gowns that are not visibly contaminated or damaged should be placed in the gown recycling/laundry bins.
- Damaged and/or visibly contaminated gowns should be disposed in the appropriate trash/waste container.



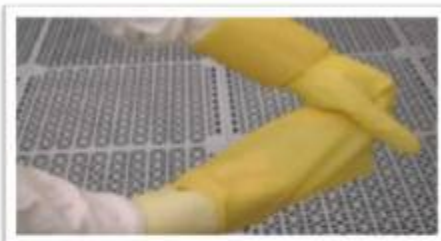
Gown Recycling Bin

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Module 3: Doffing the Gloves


Doff your gloves by turning them inside out. Disposing of your gloves in the appropriate trash or waste container.

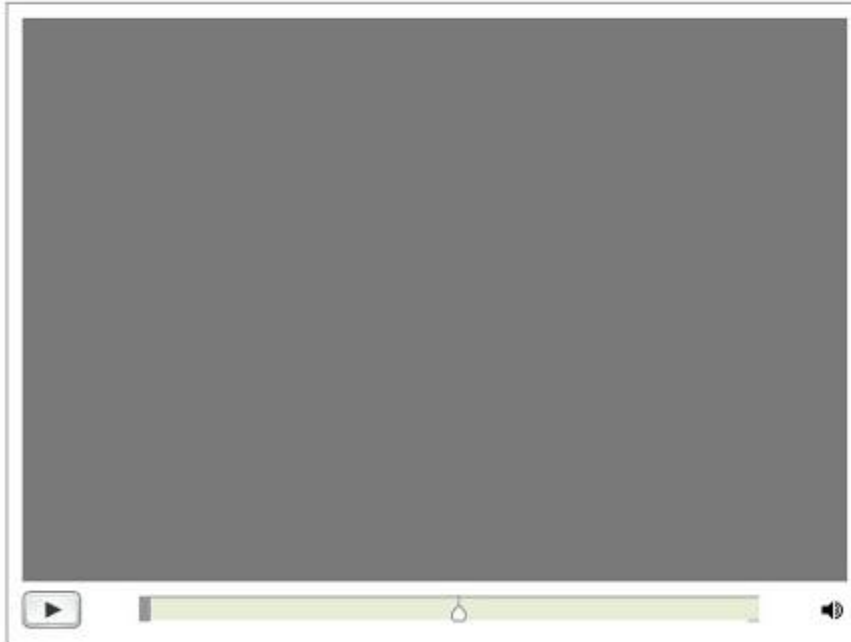


Correct way to doff your gloves

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Video Doffing PPE

Click  to view the video. Proceed to the next page after the video ends.





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Video

Video

Click  to view the video. Proceed to the next page after the video ends.





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Module 3: Emergency Procedure

In the event of a **chemical exposure** when working, do the following:

- Enter the closest safety shower and remove your PPE and clothing under running water.
- Instruct someone to call Security.
- Remain in the shower for 15 minutes.
- Comply with any directions you receive from ERT.



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Module 3: Donning/Doffing Steps

Here's a summary of the steps to don and doff your PPE:

Donning	Doffing
1. Inspect the PPE	1. Face Shield
2. Chemical Resistant Gloves	2. Chemical Goggles
3. Chemical Resistant Gown/Apron	3. Chemical Resistant Gown/Apron
4. Chemical Goggles	4. Chemical Resistant Gloves
5. Face Shield	5. Disposition items properly

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Module 4: Chemical Handling Controls

This module outlines the procedures to control exposure while handling, transporting, storing and/or disposing of chemical materials.

Follow these exposure controls for handling chemicals:

- Always wear the appropriate PPE.
- Always check the chemical label before pouring. **NEVER** use chemicals which are not labeled.
- Understand the risk associated with the chemical by reading the container Hazcom label and Safety Data Sheet/Material Safety Data Sheet (SDS/MSDS).

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Module 4: Chemical Transport

When chemicals are transported, they must be transported within splash-proof, secondary containment.

- Incompatibles chemicals such as corrosive and solvents must be segregated for transport.
- Chemical bottle caps must be in place and tightened before placing bottles into an approved cart or carrier for transport.

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Module 4: Single Bottle Transport

To transport a single bottle:

- Use an approved bottle carrier.
- Do not swing the carrier.
- Walk at a steady and slow pace.



Single Bottle Carrier

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Module 4: Multiple Bottle Transport

To transport multiple bottles:

- Use an approved cart.
- Select a cart based on the chemical's classification.
- Solvents are transported on metal carts.
- Corrosives are transported on polypropylene carts.



Metal Cart for Solvents



Polypropylene Cart for Corrosives

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Module 4: Chemical Handling Steps

Follow these steps to correctly handle and transport a bottle of chemical:

- Before moving a chemical bottle, check the label to ensure you have the right chemical and verify the bottle cap is secure.
- Grasp the throat of the bottle with one hand while supporting the bottom of the bottle with the other hand.



Correct lifting of chemical bottle

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Module 4: Chemical Pouring I

"The Pour" is one of the greatest risks for potential exposure by splash or by vapor.

When pouring hazardous chemicals,

- Check the label to ensure you have the right chemical.
- Hold the bottle with two hands, one around the neck and the other hand supporting the bottom.
- Pour carefully and slowly to eliminate splashing.
- Increase the bottle angle as you pour and keep the neck handle pointed down to control chugging.



Correct Pouring Position

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Module 4: Chemical Pouring II

- Maintain the air gap while pouring.
- Turn the bottle completely upside down to drain all liquid.
- Rotate the bottle a $\frac{1}{4}$ turn when returning the bottle right side up to prevent the liquid from dripping.
- Use dry wipes to clean up drips. Dispose of the wipes in the appropriate waste container.



Rotate Bottle $\frac{1}{4}$ Turn

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Module 4: Chemical Pouring III

- Where possible, pour chemicals in a ventilated enclosure.
- Ensure the exhaust is operating correctly by checking the monitoring device, such as Photohelic or Magnehelic.
- Work in the middle to the back of the ventilation system with your arms stretched out.
- Do not lean in towards the chemical pour or break the front plane of the ventilation system with your head.



Pouring in a Ventilated Enclosure

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Module 4: Mixing Chemicals

When mixing chemicals, ensure you do the following:

- **Always Add Acids** to water (AAA).
- **Always Add Bases** to water (AAB).
- Always mix chemicals in the order specified.
- **NEVER** mix chemicals unless you have been properly trained.
- Always utilize a laboratory hood or local exhaust system when pouring hazardous volatile materials or mixing toxic dust.

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Module 4: Waste Disposal

Waste contaminated with chemicals, such as dry wipes used to clean up drips when pouring, is often generated during PM activities.

Refer to the maintenance spec for details will detail the appropriate disposal method. Contact your supervisor or site EHS as needed for more information on waste disposal.

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Module 4: Chemical Storage

All chemicals should be stored in approved areas and/or approved cabinets.

- Do not store chemicals in bottles on the floor.
- Remove chemical materials from work areas and laboratory hoods when the chemical is not in use. 'In use' is defined as the quantity of chemical used during one shift.
- Bottles should be stored in an upright position.
- Do not exceed the storage capacity of the chemical cabinet.



Proper chemical storage

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Module 4: Chemical Segregation

All chemicals stored within the cabinet shall have a Hazcom Label attached to each bottle/container.

Keep incompatible chemicals segregated:

- Do not store acids with bases and active metals such as sodium, potassium, or magnesium.
- Do not store oxidizers with flammables, combustibles or organic material.
- Do not store inorganic acids with organic acids.
- Do not store water reactive materials with acids, bases or other products containing water.



Corrosive Cabinets



Solvent Cabinets

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Summary

Personal Protective Equipment (PPE) are devices that are used to provide a barrier between a worker and a hazard.

- PPE is effective against potential chemical exposures given that it is appropriate for the chemical, used properly, and maintained.
- PPE should be used in conjunction with proper work practices, engineering controls, and hazard awareness training.
- **PPE does not eliminate the hazard!**

To safely and correctly wear your PPE, you must inspect, don, and doff the pieces in the correct order. The steps to don and doff your PPE are:

- Donning: gloves, gown, goggles, face shield.
- Doffing: wipe down, face shield, goggles, gown, gloves.

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Summary

Handling chemicals correctly helps to prevent chemical exposure. This also includes proper chemical transporting, storage, and disposal.

- Understand the risk associated with the use and handling of a chemical by reading the product label and Safety Data Sheet/Material Safety Data Sheet (SDS/MSDS). **NEVER** use chemicals which are not labeled.
- Don the appropriate PPE and transport chemicals using the appropriate transport method.
- DO NOT transport or store incompatible chemicals together.
- DO NOT mix chemicals unless you have been trained to do so.
- Your maintenance spec will detail the appropriate chemical disposal method. Ensure you follow the spec when disposing of solid and liquid waste.
- If you have any questions, ask your supervisor or contact EHS!

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Final Assessment

You will need to pass this final assessment with a score of 100% to receive credit for this course. You will have unlimited opportunity to retake the test.

To start the assessment, click the start button below.

Start

Exit Course

REMEMBER: Personal Protective Equipment (PPE) are devices that are used to provide a barrier between a worker and a hazard.

PPE does not eliminate the hazard!

Thank you for taking this course.

Please remember to fill out the
course evaluation.

