

# OPPT N-Methylpyrrolidone (NMP) Draft Risk Assessment Final Comments of Nine Member Peer Review Panel December 31, 2013

## Gary Ginsberg (Chair)

*Question 1-1: Please comment on whether the risk assessment provides a clear and logical summary of EPA's analysis. Please provide specific suggestions for improving the clarity and transparency of the risk assessment document.*

The document is a fairly thorough and careful treatment of the potential exposures and risks presented by the paint stripping scenario involving NMP. The decisions to focus on paint stripping and the inhalation and dermal exposure pathways appear to be reasonable although as described below, more documentation of the likelihood for the dermal pathway vis-à-vis the corrosive nature of NMP on skin should be presented.

The new exposure and modeling approaches are valuable additions but have not been written up in a cohesive manner and some information appears to be missing. It would have been better if an addendum to the Dec 2012 risk assessment was prepared such that the new information was fully explained and integrated into the risk assessment.

This draft represents more than a screening level analysis as it involves BMDL and PBPK modeling, it involves detailed exposure assessment of a number of different scenarios, and the toxicology assessment relies upon a review of a number of potential endpoints from different studies, with PBPK modeling used to ascertain which endpoints and dose metrics appear to be most consistent across studies and dose routes. The graphics are particularly good in showing the exposure pattern with each scenario in relation to acute risk benchmarks. The scoping phase included a sensitivity analysis to determine which exposure scenarios needed evaluation.

The document could be improved by describing the paint stripping protocol that is being simulated by the exposure models. What are the label instructions, what is common industry practice, what are high end or extremes in stripper use. It would be helpful to describe the stripping protocol in terms of the various steps, e.g., stripper is opened, (container left open entire time?), applied to rag or brush or sprayed on, applied over certain sized surface area, gloves used (or not – what do the surveys show?), hands washed (or not?), abrasive techniques used? times involved in each step, method to remove loosened paint, cleanup procedures, etc.) Page 82-86 of App C is a useful general description but does not provide a synthesis protocol that would lead to concrete exposure assumptions.

Questions have been raised about the need to do a dermal risk assessment based upon NMP corrosivity. The draft risk assessment also mentions that NMP is corrosive (e.g., Executive Summary Page 13) and that this property creates uncertainty regarding the dermal exposure estimates. However, the toxicology section (App E, page 149) states that NMP is a mild eye and skin irritant in rabbits and that it is not irritating in humans to eyes or respiratory tract but it is irritating to skin. This is not the description of a corrosive compound or one that would drive

extensive use of gloves. The draft document does not mention whether survey information is available regarding worker use of gloves when handling NMP products. Such survey information may help determine the likelihood that the “no gloves” scenario actually occurs. In any case, the document needs to decide whether NMP is corrosive and present these data and references.

The Executive Summary mentions that recent studies have decreased concerns for reproductive effects. However, this is not reflected in the text or Appendix E. What was the original concern and what new data has decreased this concern? Is USEPA aware of Sitarek et al. 2012 (*Birth Defects Res B Dev Reprod Toxicol.* 95: 195-201) which according to the abstract is a one generation rat reproduction study of NMP which found significant decrease in fertility at 450 mg/kg/d and impaired pup viability and development at the lowest dose tested (150 mg/kg/d). This study was not mentioned in the draft document perhaps because it involved the oral (gavage) route of exposure. However, the draft document mentions that the oral and dermal route has similar acute toxicity as evidenced by LD50 data (page 45), so it is logical to conclude that the Sitarek et al. oral one generation reproduction study is relevant to dermal and perhaps inhalation as well.

***Question 1-2: Please comment on whether appropriate background information is provided and accurately characterized. Please provide any other relevant literature, reports, or data that would be useful to support the risk assessment.***

Any additional literature I provide is with respect to specific charge answers.

***Question 2-1: Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of the workplace inhalation exposure, including specific citations (if available) of data sources characterizing occupational inhalation exposures.***

As described in my response to Question 9-5, it would appear that reliance on graffiti workers as the sole source of workplace exposure concentrations creates a large uncertainty and potential for underestimation of exposure.

***Question 3-1: Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of consumer inhalation exposure, including specific citations of data sources characterizing consumer emission profiles of NMP-based paint strippers. As part of the review, please also evaluate the sensitivity analysis conducted for the assessment and comment on the strengths and weaknesses of the evaluation of different exposure scenarios and the choice of assumptions/input parameters for generating central tendency and upper-end NMP air concentrations.***

The consumer modeling was carefully done and presents different scenarios in order to capture a range of exposures. The predicted air concentrations comport with the limited occupational (indoor) data and are greater than the outdoor graffiti data. Thus the modeling of residential applicators would appear to be reasonable. The prediction for the rest of the house may be informed by household exposure models for other chemicals. For example, radon concentration differences according to floor of the home have been measured in numerous studies – my general

recollection is a three-fold lowering of concentration for every floor of the house (e.g., 2nd floor would be 10-fold lower in concentration than the basement). This type of information could be used as a general check of the ROH estimates.

The sensitivity analysis to derive exposure scenarios is a good idea and one that works to achieve a range of realistic exposures. However, in deriving exposure scenarios, the identification of a standard step-by-step paint stripping protocol would clarify what is being simulated and what the options for alternative assumptions might be. For example, is it possible for a residential applicator to have two pieces of furniture undergoing the stripping process in the same workshop just slightly staggered in time?

Predicted air concentrations are presented in Table 3-7. However, the presentation is confusing as the scenario description states that it is pertinent to the user or non-user but then that category is further broken into two lines for user and non-user. If the scenario is already specific to the user or non-user, then why are the results further subdivided into user and non-user?

***Question 4-1: Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of the workplace dermal exposure, including specific citations (if available) of data sources characterizing occupational dermal exposures. Please comment on the strengths and weaknesses of the evaluation and the choice of assumptions/input parameters for generating estimates of the NMP's dermal exposure.***

The revised exposure modeling is improved in including dermal uptake of vapors and combined dermal and inhalation exposure.

The differences in dermal exposure between the residential applicator and the worker applicator are substantial with the reason not clear. Since direct contact between NMP and applicator hand should not vary between worker and home applicator when gloves are not worn in either case, it is curious that the exposure dose is different between these two scenarios. Contributing to this difference is that for some reason the at home applicator has an exposed hand surface area of only 490 cm<sup>2</sup> while the worker has 840 cm<sup>2</sup> SA of exposure. Further, the content of NMP in the product is assumed to be less in the home product than in the workplace stripper. Yet in spite of these assumptions that would make the home applicator less exposed, the daily dermal dose is considerably higher in the home application. The major factor for this seems to be the amount of NMP on the skin. The film thickness approach is used for the residential applicator (0.03 cm thickness x 490 cm<sup>2</sup> SA x 1.1 gm/cm<sup>3</sup> = 16.2 gm/day on skin and absorbed) while the surface density approach is used for the worker (up to 2.1 mg/ cm<sup>2</sup> skin\* 840 cm<sup>2</sup> skin = 1.76 gm/d on skin and absorbed). This creates a 10-fold greater direct contact for the home applicator. No rationale is presented which would support this difference in exposure calculation approaches or results.

As discussed below under PBPK modeling, the dermal uptake rate associated with liquid NMP contact is not clear but its possible USEPA is assuming immediate (100%) absorption, akin to a bolus dose. Alternatively, they may be using the vapor uptake rate derived by Poet et al. which is a very fast rate, or the rat dermal uptake rate from 2003, which is a much slower rate. This should be clarified and the dermal model for vapor as opposed to liquid NMP be explained more

completely. A rate would be preferable to a bolus uptake but it may be difficult to determine a rate without any human calibration data for liquid NMP contact.

***Question 4-2: Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of the consumer dermal exposure, including specific citations (if available) of data sources characterizing dermal exposures in a residential setting. As part of the review, please comment on the strengths and weaknesses of the evaluation and the choice of assumptions/input parameters for generating estimates of the NMP's dermal exposure.***

The considerations described above for worker dermal exposure carry over to the consumer dermal scenario. In particular, the film thickness of 0.03 cm appears to be excessive relative to the surface density approach, but it is difficult to tell which is more accurate. In either case, I would recommend the two approaches be harmonized unless there is clear rationale for different modeling approaches for consumers vs. workers.

***Question 4-3: Please comment on the assumptions used by the Agency regarding film thickness for the assessment, including any additional data on film thickness with which to assess dermal exposure to NMP for both consumers and workers.***

Film thickness appears to be a function of NMP formulation as it affects viscosity and other properties of the stripper. This parameter would appear to be particularly uncertain due to variations in product formulation. If possible, the range of possible values should be used in sensitivity analysis rather than a single value if the film thickness concept moves forward. The other alternative, surface density on skin, which is the approach for workers, is not well documented in the current model. The range of possible values (0.7 to 2.1 mg/cm<sup>2</sup>) is referenced to an EPA/OPPT 2 Hand Dermal Contact Model which is not cited as to publication date or web location. The USEPA dermal guidance from 2007 (EPA 600/R-07/040F, September 2007, [www.epa.gov/ncea](http://www.epa.gov/ncea)) presents this range of surface density for the two hand model but does not provide supporting documentation. This is needed to improve confidence in the range assumed in this step of the assessment and to determine whether it should carry more weight than the film thickness approach.

***Question 5-1: Please comment on EPA's use of the identified developmental studies and POD to assess acute inhalation exposures to NMP use in paint strippers. As part of the review, provide your input on the appropriateness of using an acute POD based on fetal body weight decrements that were observed in the presence of maternal body weight decrements following exposure to NMP during gestational days 6 to 13. Please comment on whether the maternal no-observed-adverse-effect level (NOAEL) of 122 mg/m<sup>3</sup> (Saillenfait et al. 2001, 2003) should be analyzed in the MOE calculations along with the fetal body weight decrements. Please specify any other endpoints that should be considered for the hazard evaluation of acute inhalation exposures. Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.***

The Toxicity assessment was correct in relying upon developmental endpoints for both acute and chronic NMP risk assessment. The document conservatively assumes that developmental testing results are applicable for acute (4-hr exposure) risk assessment without adjustment. While

acknowledging that the testing vs. human exposure timeframes do not line up, the document justifies the acute use of repeat dose studies without adjustment based upon a review and analysis by van Raaij et al. 2003. The draft document chose to focus on the fetal body weight data from van Raaij et al. 2003 as this is one of the key endpoints in the NMP risk assessment. Van Raaij et al. 2003 show that when comparing over 22 chemicals which studied the effects on fetal body weight in single dose as compared to gestational exposure, the average NOAEL is 3.4 times higher and the average LOAEL is 4.76-fold higher in the single (acute) studies. This analysis appears to better support the use of 2- 4-fold factor in going from the rat developmental studies to an acute POD rather than the conservative no adjustment approach. This is for the fetal body wt parameter which is believed to be decreased as a result of ongoing stress to the maternal and/or fetal system, rather than the result of an acute effect during a critical window of exposure. An additional consideration is that since fetal resorptions are part of the NMP fetotoxicity profile, one could draw from van Raaij et al. 2003 the resorption data as an additional point of comparison between single exposure (acute) and gestational potency. Additionally, the comparison related to skeletal abnormalities is somewhat different. But if going strictly on fetal body weight as an endpoint, I would recommend an adjustment of 3- or 4-fold (actually the median of the studies in Table 5 of van Raaij, et al. 2003 may be more like 3-fold but this should be checked).

As described below in Question 9, it appears that maternal body weight in the Sallienfait inhalation study (2003) may be the most sensitive indicator of NMP effect on the maternal-fetal system and provides a statistically significant response at a dose which also appears to impair fetal growth, although the fetal endpoint was not statistically significant at that dose level. The maternal body weight appears to be part of a continuum of NMP developmental toxicity and so should not be discounted. The potential to use skeletal abnormalities is also discussed under Question 9.

***Question 6-1: Please comment on EPA's use of the identified developmental studies and POD to assess chronic inhalation exposures. As part of the review, please comment on the appropriateness of using a developmental toxicity endpoint and the identified effects to assess chronic inhalation exposures to NMP-based paint strippers. Please specify any other toxicological endpoints that should be considered for the hazard evaluation of acute inhalation exposures. Also, please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.***

The extrapolation of developmental rat results to chronic worker exposures without adjustment is reasonable as this has been done on IRIS for compounds such as methyl mercury and trichloroethylene. The concept being that the developmental endpoint may be more sensitive than other more chronic exposures and so an RfD based upon this endpoint would be protective of other types of non-cancer effects as well. However, to use this approach without database uncertainty factors, a data gap/uncertainty analysis should be performed and the lack of a database uncertainty factor justified.

The reproductive testing conducted on NMP should be brought into focus vis-à-vis new oral results from Sitarek et al. 2012 relative to the Solomon et al. 1995 finding of little developmental risk from inhalation exposure.

## Reference:

Sitarek K, Stetkiewicz J, Wąsowicz W. 2012. Evaluation of reproductive disorders in female rats exposed to N-methyl-2-pyrrolidone. *Birth Defects Res B Dev Reprod Toxicol.* 2012 Jun;95(3):195-201.

***Question 7-1: Please comment on EPA's use of the identified developmental study and POD to assess acute and chronic dermal exposures. As part of the review, provide your input on the appropriateness of using a developmental toxicity endpoint and the identified effects to assess acute and chronic dermal exposures to NMP-based strippers. Please specify any other endpoints that should be considered for the hazard of acute or chronic dermal exposures. Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.***

The developmental dermal study of Becci et al. 1982 has the advantage of being by the appropriate dose route for assessing human dermal exposures and it is consistent in finding similar developmental effects as found by Sallienfait et al. in inhalation (2003) and oral NMP dosing (2002). USEPA uses the high dose (750 mg/kg/d) as the LOAEL and 237 mg/kg/d as the NOAEL although the mid dose did show a suggestive skeletal abnormality increase in a dose response concordance with the high dose (mid dose not significant). The benchmark dose derivations discussed below utilize all the data and thus are preferable to a LOAEL/NOAEL treatment. Further, use of internal dose metrics rather than external dose obviates the need to restrict the dermal risk assessment to dermal toxicology studies, especially where the exposure dose is cumulative across dose routes. Therefore, Becci et al. 1982 is properly seen in the revised USEPA analysis as part of the overall developmental toxicity information that can inform dose response independent of dose route.

***Question 8-1: Please review the model and comment on the Poet et al. (2010) analysis as well as EPA's evaluation of the revised model. Please comment on whether the model is clearly and transparently described and technically and scientifically adequate for supporting OPPT's workplan risk assessment for NMP-based paint strippers. Specifically, please address the structure of the PBPK model, parameter calibration and model predictions of the available in vivo data.***

The Poet model as reported in Toxicological Sciences 2010 is comprehensive in modeling various uptake routes, modeling both parent compound and metabolite and relying upon several different human and rat PK datasets. The model parameterization of uptake and biochemical (metabolism) constants are based upon sufficient empirical data to allow backfit against a calibration set and then evaluation against different studies for humans. For rats, it appears that while several datasets are available, they are all by different dose routes and so they are calibration exercises. Those figures show that the constructed model is able to reproduce the underlying data and so is likely to also be reasonable for predicting internal dose metrics in the rat developmental studies conducted by inhalation (e.g., Sallienfait et al. 2003) and oral exposure (e.g., Sallienfait et al. 2002). However, it is unclear that the rat modeling presented in Poet et al. 2010 adequately predicts the dermal exposure route as the calibration to the Payan et al. 2003 dermal uptake dataset is not shown. Human PK data include studies involving whole body and dermal only as calibration, although the dermal was exposure to vapor rather than liquid and so it does not appear that a human dermal/liquid contact dataset exists. It's unclear whether the rat

(Payan et al. 2003) dermal uptake dataset is used to also predict human skin uptake from liquid NMP contact. Given that the other human datasets used for validation purposes also did not involve skin contact with liquid NMP (except in one subject who had dermatitis in spite of using gloves), a datagap would appear to exist with respect to modeling human dermal uptake of liquid NMP. Given the importance of this pathway to the human risk assessment and given the huge difference in uptake rate between vapor and liquid skin contact (Poet et al. Table 2 parameters), it would appear that this is a substantial uncertainty. USEPA's simulation of the dermal route in humans appears to appropriately consider vapor exposure according to the rate constant provided in the Poet et al. 2010 calibration of the Bader et al. 2008 experiment. However, the uptake of liquid NMP across the skin appears to involve a bolus uptake of 100 percent of what is on the skin during a one time per day exposure event with either a given surface density or film thickness on the skin. Dermal absorption is expected to be rapid from contact with the liquid but not having a rate and assuming everything on the skin is taken up immediately may cause an overprediction, especially with respect to Cmax. If USEPA used a more graduated dermal uptake rate (e.g., from the rat dermal study), that should be stated. The current documentation available to the panel does not indicate so; at the November 8th panel meeting this subject came up with USEPA and it appeared that dermal absorption was modeled as a bolus rather than a rate based upon the very rapid uptake seen in Bader. However, that was human exposure to NMP vapor, not liquid. So this needs to be clarified and perhaps modified using the rat dermal uptake rate based upon Payan et al. 2003 or other considerations.

The model fits provided by Poet et al. 2010 look reasonable with the whole body model (dermal vapor +inhalation) simulations of the human datasets important confirmations that real world exposures are well simulated. While these fits are reasonable according to the published version (Poet et al. 2010) we understand that there were errors in reporting parameter values in that manuscript that could have affected model runs. With the Poet et al. 2013 corrections and the USEPA runs of the revised NMP model, USEPA reports reasonable fits to the data. However, the panel did not have access to the runs of the revised model so it is not possible for us to independently determine whether the current model performs adequately. I recommend that USEPA create a formal PBPK model addendum to the December 2012 risk assessment which describes differences between the revised and original Poet models, performance of the revised model, and then how it is applied to develop internal dose metrics for dose response assessment of human scenarios.

Dale Hattis brought up a non-linearity in the Bader et al. human dataset in that with increasing doses the amount of parent compound/unit external dose decreased rather than increased. This type of non-linearity is not captured in the current kinetic constants and may need to be addressed as it may portend greater parent compound at lower dose than with the current (revised Poet) model. I support USEPA efforts to evaluate model fits across the range of human data (e.g., Akesson and Paulsson, 1997).

***Question 8-2: Please comment on the appropriateness of using the selected dose metric for chronic inhalation and dermal exposures based on the maternal blood concentration of the parent compound expressed as the area under the curve (AUC). Please comment on whether the maternal dose metric is a reasonable surrogate for a fetal dose metric in the absence of fetal metabolism data.***

Parent compound AUC is the appropriate dose metric for evaluating endpoints such as fetal or maternal body weight which are related to multi-day effects; skeletal aberrations such as delayed ossification may also be related to generalized toxicity and developmental delay while frank malformations may be related to a more acute, specific window of vulnerability effect which may relate more to Cmax. The van Raij database for skeletal effects indicated that for the majority of compounds for which acute (single day) vs. gestational data are available, that a substantial difference exists between dose response for repeat dose vs. single day of dosing (less potent). However, there were examples where there was no difference suggesting that in certain cases a single day of dosing may be sufficient to produce as much risk as repeat dosing. For those compounds, Cmax may be the preferable dose metric. For NMP and skeletal effects this is an uncertainty.

As noted above, Cmax predictions for the human dermal scenario may be more uncertain than AUC descriptions of this scenario so on that score AUC may be preferable to Cmax.

Review of the EPA document: “Using Internal Dose-Response Comparisons to Identify Dose Metrics Which Best Correlate With Toxicity (Version 09/16/13)” – it becomes evident that there are advantages and disadvantages to using different dose metrics with different toxicity endpoints. If the skeletal aberrations endpoint becomes the preferred approach, the dose response modeling should include more than Becci et al. 1982 and Sallienfait et al. 2003, but also the oral data from Sallienfait et al. 2002. The oral data fill in some important dose response data points where effects are actually found rather than relying upon the combined Becci/Sallienfait 2003 dataset in which there is only one statistically significant datapoint, as is now proposed. The Figure 1 plots which compared dose metrics for the skeletal endpoint across studies claims to have found a better fit with the Cmax metric. However, this better fit was not statistically confirmed and there doesn't seem to be that much difference across the three dose metrics in Figure 1. Thus, even for skeletal aberrations I would not consider Cmax as preferred without further justification.

The maternal dose metric is a reasonable surrogate for fetal or cord blood NMP levels.

***Question 8-3: Please comment on whether the selected dose metric for acute inhalation and dermal exposures should be reported as the maternal blood AUC of the parent compound and/or the maximum concentration (Cmax) in maternal blood.***

As discussed in the preceding question, the preferred endpoint is AUC24 hr.

***Question 8-4: Please comment on whether the BMD analysis should be conducted with the PBPK-derived internal doses or the external air concentrations (standard approach) reported in Sallienfait et al. 2003. Please specify whether the BMD calculations (Appendix F of draft risk assessment) were appropriately conducted and documented.***

BMD analysis is better done with PBPK-derived internal doses as these more readily enable combination of inhalation and dermal exposures in the human exposure scenarios. They also provide a better comparison across species. I share the concern raised by Dale Hattis that the rejection of some BMD models based upon the BMDL three-fold rule needs greater justification.



***Question 9-1: Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the acute inhalation risks to consumers of NMP-based products and to bystanders/non-users (e.g., children, women of childbearing age), including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HECs. Please comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the acute inhalation risks.***

The MOE approaches in risk characterization depend upon 5 aspects: 1) dose response assessment of the underlying toxicology data; 2) exposure time adjustment to go from the animal test protocol to the human exposure scenario; 3) dosimetric adjustment to extrapolate across species and dose routes; 4) application of MOE factors that captures the uncertainty in extrapolating kinetics and dynamics across species and across individuals within a species and other toxicology uncertainties. 5) Consideration of uncertainties in the exposure analysis.

- 1) The dose response assessment for acute risks appropriately relies upon the developmental endpoint from testing in rats. However, as described above, the assumption of equal dose response when going from gestational exposure in a rat to 4 hours in a human may be inappropriate and using a POD that is 2-4-fold higher is supported based upon the review and analysis conducted by vanRaij et al. 2003. The dose response for fetal body weight in Sallienfait is a good choice for risk assessment but the data (especially for female offspring) show a continuous downward bodywt trend with increased dose. Thus, it is difficult to say with confidence that the effect begins with the high Sallienfait et al. dose. The decision to use BMDL05 is not justified and as that is a fairly substantial body wt effect and as aBMDL01 would be a more sensitive effect level further up the dose response curve, it may be preferable. Another approach is to just use maternal body wt effects as reported by Sallienfait et al. 2003. The maternal effect is seen at the mid dose with statistical significance only at one time point but the overall trend is rather evident. The mid-dose is also where there is evidence (but not statistically significant) of fetal body weight effects. Maternal body weight in other studies may not be as useful an endpoint as the Becci et al dermal study showed decreases in maternal body weight but that protocol did not run for the entire gestation and so there may have been time for recovery of this parameter. The oral NMP study by Sallienfait et al. 2002 involved decreases in both food consumption and body weight at the two highest doses and given the dose route (dietary), one has to be concerned that some of the body weight loss was an aversion to the test diet. The Sallienfait maternal body weight effect at the mid dose was without a statistically significant effect on food consumption and of course, being by the inhalation route, is not going to create a dietary aversion problem. Thus, maternal body weight in Sallienfait et al. 2003 would appear to be a reasonable choice for endpoint selection and dosimetric analysis.
- 2) Exposure time adjustment: the use of PBPK modeling automatically corrects for hours/day adjustments as it is the internal AUC rather than inhaled concentration that drives the dose response. However, the time adjustment between gestational exposure vs. the human 4 hour exposure continues to be an outstanding issue as described above.
- 3) Dosimetric Adjustment: my preference would be to use AUC for maternal body wt effects from Sallienfait 2003 as the primary dosimeter, followed in preference by AUC for fetal body wt (Sallienfait et al. 2003) at the BMDL01, followed by AUC for skeletal effects from a combination of Becci, Sallienfait 2003 and Sallienfait 2002.

- 4) MOE factors: The MOE of 30 appears to be appropriate. However, there has not been a comprehensive data gap analysis to determine whether substantial uncertainties exist in the database. For example and most relevant to the acute scenario, we have no data regarding acute irritation or CNS effects. The workplace literature on NMP may give some idea of whether it elicits an acute response and at what level. Laboratory animals cannot tell the investigator when they have a headache. The low odor threshold relative to the modeled concentrations suggest that applicators and residential bystanders will detect the NMP odor which in some individuals may trigger an irritation response. These considerations can be part of a data gap analysis.
- 5) Exposure issues – it is an improvement that the inhalation scenario now has vapor uptake across the skin in both the acute and worker exposure scenarios. Further, it is an improvement that dermal is considered separate and then combined with inhalation. However, the potential for children to receive a higher dose due to increased surface area and respiratory rate per body weight, as well as the potential for slower metabolism of parent compound, has not been evaluated.

***Question 9-2: Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the chronic inhalation risks to workers using NMP-based products, including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HECs. Please also comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the chronic inhalation risks.***

The analysis of chronic worker risks is similar to the acute inhalation risk in terms of studies, endpoints, PODs, BMDLs and MOEs. Therefore, responses to charge question 9-1 apply here as well. The datagap analysis might focus on repeat dose or chronic endpoints that may be missing or not as thoroughly examined such as reproductive toxicity. Of note is the recent Sitarek et al. 2012 study (*Birth Defects Res B Dev Reprod Toxicol.* 95: 195-201) which according to the abstract is a one generation rat reproduction study of NMP which found significant decrease in fertility at 450 mg/kg/d and impaired pup viability and development at the lowest dose tested (150 mg/kg/d). This study was not mentioned in the draft document perhaps because it involved the oral (gavage) route of exposure. However, the draft document mentions that the oral and dermal route have similar acute toxicity as evidenced by LD50 data (page 45), so it is logical to conclude that the Sitarek et al. oral one generation reproduction study is relevant to dermal and perhaps inhalation as well. The Solomon et al. 1995 two generation rat reproduction inhalation study found very little effect but some suggestive evidence for a post-partum depression in pup body weight that was discounted on the basis of inconsistent dose response. It would be of interest to compare the Sitarek results to the Solomon results on an internal dose basis given that they represent different dose routes. The gavage route of exposure in Sitarek may be relevant to the dermal route given the speed with which NMP can be taken up across the skin and the potential for large contact rates in the paint stripping scenario.

***Question 9-3: Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the acute dermal risks to consumers of NMP-based products, including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HEDs. Please also comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the acute dermal risks.***

The acute dermal risk estimates for the residential scenario stem from the same array of toxicology studies and endpoints as discussed above, with similar PBPK modeling issues. The MOE factor of 30 fold appears to be appropriate. Note that if the key endpoint for dermal risk is the Sallienfait inhalation data (fetal wt or maternal body wt) then that will involve a dose route extrapolation. In fact, any internal dose metric for the dermal pathway will involve modeling of the dermal uptake from liquid contact with the skin. As mentioned above, this pathway has no calibration or validation data other than the Payan et al. 2003 study in rats, which had a rather low rate constant. It appears from the documentation available that USEPA is using a bolus (immediate) uptake of liquid NMP from the skin with a 100 percent uptake percentage but no rate term. This may lead to errors, particularly in Cmax. The Poet et al. 2010 manuscript did not simulate this type of human exposure. The option of extrapolating from the Becci et al. study based upon external dose and a metabolic scaling factor would also be reasonable.

***Question 9-4: Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the chronic dermal risks to workers of NMP-based products, including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HEDs. Please also comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the chronic dermal risks.***

Chronic dermal risks to workers involves the same array of POD and modeling issues described above for the other scenarios. The lack of chronic toxicology studies by the dermal route represents a data gap but this may be considered minor relative to the availability of other types of dermal and inhalation testing.

***Question 9-5: Please comment on whether the risk assessment document has adequately described the uncertainties and data limitations in the methodology used to assess risks to allow the EPA to reduce risks to human health from NMP. Please comment on whether this information is presented in a transparent manner.***

A number of the uncertainties in the NMP risk assessment are well described in a qualitative manner by USEPA but not in a quantitative or semi-quantitative manner. Quantitative probabilistic characterization of variability or uncertainty is not necessary in every risk assessment and in the current case, given the range of exposure and modeling scenarios run, it is likely that a reasonable array of different risks have been presented. This includes different user behaviors and different levels of protection (gloves on or off, respiratory protection or not). Running MOE analyses on all these exposure and modeling options as presented in the latest round of Excel spreadsheets from USEPA will end up with a potentially confusing array of risks. Therefore, it will be important for USEPA to communicate these clearly and perhaps sort thru the results to highlight 1) what scenarios and behaviors create the greatest risk; 2) what may represent the most likely risks; 3) what are the greatest contributors to risk (e.g., inhalation vs. dermal vapor vs. dermal liquid contact).

Regarding a more informative description of uncertainties, USEPA can consider an over/under approach in which best professional judgment is used to state whether a given uncertainty is likely a source of over-estimation (e.g., using gestational data for a 4 hr acute human exposure without adjustment; immediate dermal absorption of 100% of NMP on skin), under-estimation (omission of children; too little time assumed for stripping activity; one contact per day based

upon NMP corrosivity but that corrosivity not well established) or unclear (toxicology data gaps). This could help the reader understand whether overall, the assumptions and uncertainties tend to go in one direction or the other. Another approach is to identify the risk drivers (e.g., time spent actually doing the stripping) and describing the range of values used vs. the range of all values possible and the uncertainty in the underlying data.

Uncertainties incompletely addressed in the draft NMP risk assessment:

- 1) Potential for the bystander exposure to be a young child, with attendant greater skin surface area, respiratory rate and slower NMP metabolism. Does the 10 fold intra-human uncertainty factor cover these possible children's factors. It is common for some risk assessments involving children to encompass the greater exposure dose received by children where this can be known (e.g., soil ingestion rates per body wt; pesticide risk assessment). If children are not quantitatively evaluated in the current risk assessment, the uncertainty they present should at least be described. One factor that could decrease concern for children is that the toxicology endpoint would suggest pregnant woman would be the most vulnerable receptor. However, developmental endpoints may pertain to postnatal windows of vulnerability even though the testing is not typically adequate to describe this risk. The reproductive studies of Sitarek et al. 2012 and Solomon et al. 1995 involved postnatal exposure but this was via breast milk and it is unknown to what degree NMP is available in breast milk.
- 2) Potential toxicological data gaps or uncertainties presented by the underlying data as described in preceding sections. For example, the acute neurotoxic potential of NMP is not discussed. Given the relatively high concentrations simulated, much higher than the NMP odor threshold, it is possible that there could be acute irritation and neurological effects. This possibility should be considered from the perspective of surveys and reports from the workplace and any other studies or clinical reports.
- 3) The extrapolation between gestational developmental data to acute exposure scenarios – the van Raij reference is an excellent resource and could be used to greater purpose in the current risk assessment.
- 4) USEPA identifies one episode of dermal contact/day as an uncertainty. It would seem that the uncertainty of this assumption could be addressed in more depth. USEPA apparently assumed this largely because of NMP corrosivity which would preclude further dermal contact after the initial reaction. However, the risk assessment document does not well support this concept mentioning NMP corrosivity in passing in several places in the text but then in Appendix E NMP skin reactions in rabbits are described as mild. Thus this needs to be clarified but that would seem to be a weak justification. Rather, the one contact/day assumption seems reasonable to me because it is likely that from a single contact event some NMP liquid will wipe away, be washed away, volatilize away or be absorbed so that assuming full absorption of the single event accounts for losses on the one hand (used figuratively here) and multiple contacts on the other over the course of the workday or residential project.
- 5) The air concentrations assumed for workers are based upon a limited amount of data for outdoor graffiti removal workers. These air estimates are considerably lower than the air estimates for the residential scenario, even the non-user. This discrepancy may be due to the indoor/outdoor exposure differences. However, there would appear to be many workers that would be handling NMP indoors. Thus, the use of graffiti workers as the occupational basis would present a rather large uncertainty and potential for

underestimation. The MCCEM model applied to a small workshop occupational setting may be appropriate to decrease the uncertainty surrounding worker air concentrations. This could be a screening level analysis to help bridge the gap between the graffiti worker data vs. the MCCEM results for residential scenarios and the limited occupational and chamber data for NMP exposure in indoor workplaces (Appendix C). As pointed out by USEPA on page 91, An EU report states that there is “probably...no fundamental difference between the application of paint removers by professional painters and consumers” – therefore, one should expect a similarity in exposures across the consumer and worker exposure scenarios on an acute basis. I would think that USEPA could consider extending the consumer MCCEM model to a variety of workplace scenarios on the basis of: 1) the NMP emission factors developed by simulation of the single NMP trial (Appendix D, using data from USEPA 1994b) can be applied not only to consumers but also to workers. This may be especially so for the furniture stripping industry as the MRI 1994 study involved NMP-based stripping of painted wood boards. This would take care of “release fraction” in the table below; 2) application rate – given the EU comment above, the application rate may be assumed to be similar between consumers and workers; 2) NMP formulations used in workplace vs. consumer settings – a quick survey of how these may vary with particular emphasis on the furniture stripping industry would seem reasonable; 3) consider whether surface area treated to room air volume will differ greatly across industries and scenarios; it appears logical that the size of the workspace will need to comfortably accommodate the size of the item being stripped such that small jobs can be in small workshops and large items (automobiles, airplane parts) in large spaces. However, the ratio of surface area stripped to room size may not be so variable; given that USEPA is focusing on small shops anyway, it may not be such a large extrapolation from the consumer to the workplace especially if limited to something like furniture stripping; room ventilation – continue assuming an open window seems reasonable. Another thought is that the NMP extrapolation from consumer MCCEM modeling to workplace exposures can be informed by the DCM MCCEM model results vs. industry exposure. There is no reason to think that changing the stripping chemical will change the relationship between MCCEM results and actual occupational exposures, although it is recognized that there are uncertainties with both estimates and that using a ratio may compound the inherent uncertainties.

## **Thomas W. Armstrong**

**Issue 3. Question 3-1:** Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of consumer inhalation exposure, including specific citations of data sources characterizing consumer emission profiles of NMP-based paint strippers. As part of the review, please also evaluate the sensitivity analysis conducted for the assessment and comment on the strengths and weaknesses of the evaluation of different exposure scenarios and the choice of assumptions/input parameters for generating central tendency and upper-end NMP air concentrations.

**Main Comment.** The EPA Draft Risk Assessment for NMP uses an incorrect value for the first order exponential decay constant (K1) of 10 per hour (0.17 per minute) for NMP. Since this may

be difficult to believe, this commentary goes into considerable detail to demonstrate the error is real and has significant impact in the Draft NMP RA. The second exponential decay constant (K2) for NMP appears approximately appropriate. The K1 of 10 per hour is the same value used for DCM in the Draft DCM RA. This K1 is an appropriate value for DCM, but is very erroneous for NMP. The vapor pressures, a prime determinant of K's, are vastly different. This K1 is a parameter error used in the NMP modeling for Scenarios 1 to 8, and is unfortunately not just a typographical error in the list of parameters in the tables. **The “downstream” work on NMP Margins of Exposure and other subsequent analyses using the results of Scenario 1 to 8 are then also significantly in error and will need to be redone.**

The error dramatically shifts the shape of the Concentration versus Time series for the scenarios so that maximum concentrations generally (but not always) occur after the consumer leaves the work zone. This means the correct personal exposure profiles will be dramatically lower than the erroneous results given in the current NMP draft. The peak concentrations are also significantly affected, but perhaps not quite as dramatically.

Since the MCCEM model install files do not work with current the Windows versions available to this reviewer, another modeling tool was used to generate results to compare to the MCCEM output. The tool is derived from a spreadsheet that led to an American Industrial Hygiene Association tool, IH Mod (available at: <http://sp4m.aiha.org/insideaiha/volunteergruops/EASC/Pages/EASCTopics.aspx>) The spreadsheet developed for this review uses two of the models, the Well Mixed Room with Exponentially Decreasing Emission Rate and the Two Zone Model with Exponentially Decreasing Emission Rate. Both have been expanded to consider the second exponential (K2) for NMP and to avoid reporting concentrations above saturation. Note in some of the models, the K2 series contributes significantly to the exposures over time after the application of the stripper.

**The comparative modeling is admittedly a bit rough, but should be sufficient to convince knowledgeable exposure modelers that a) the error for the value of K1 did in fact occur and b) the incorrect K1 in the modeling propagate significant errors in the rest of the NMP RA that utilizes the consumer Scenario 1 to 8 results. Anyone who used MCCEM without a good understanding of the theory and appropriate parameter values may not readily understand the effects of the error.**

### **Comparative Modeling Results to Demonstrate the K1 Error.**

One of the first indications of the error arises from Figure D-5 in the NMP Draft Risk Assessment (see Item 1 below). Another indication is that a K1 of 10 per hour (0.17 per minute) means approximately 17 percent of the initial NMP mass evaporates in the first minute, and 17 percent of the amount remaining each minute thereafter in an exponentially decreasing manner. This 17 percent in the first minute is obviously not correct and not plausible given NMP's low vapor pressure. Several scenarios from the NMP draft RA are examined to illustrate the effect of the error, but the following is not a complete examination of all the modeled NMP scenarios. Rather, the intent is to demonstrate how the wrong K1 of 10 per hour and a more appropriate K1 of 0.3 per hour alter the peak concentration and concentration versus time results. Note 0.3 per hour is an estimate and a proper analysis of Figure D-5 may lead to a slightly different value.

1. The exposure chamber (MRI, cited as EPA 1994b) results cannot be replicated with the incorrect K1 of 10 per hour (0.17 per minute). They can be adequately replicated with a

- K1 of 0.3 per hour (0.005 per minute), which is much more a reasonable value for a low vapor pressure material like NMP. See attachment, figures in items 1, 2 and 3.
2. The MCCEM bathtub refinishing scenario results for NMP can be approximately replicated using the incorrect K1 of 10 per hour (0.17 per minute). Using the more appropriate K1 value of 0.3 per hour (0.005 per minute), the results are dramatically lower and do not approach saturation at Cmax. See figures in attachment, items 4 to 6. This is much more in line with expectations for NMP based on the chamber data and other real world data.
  3. As an additional spot check, an attempt to recreate the results for Scenario 1 is included in the attachment. Note that use of the INCORRECT K1 of 10 per hour reasonably but not exactly compares to the reported MCCEM results. If a more appropriate value of 0.3 per hours is used for K1, the results are dramatically different, for Cpeak as well as the shape of the C vs. t curve.
  4. With a K1 of 10 per hour, the MCCEM model predicted concentrations above saturation in the source cloud. The modeling team recognized this as a problem and overrode that nonsensical result by truncating the curve at saturation. The spreadsheet model used of r this critique encountered the same issue with the K1 of 10 per hour, and this is also corrected for. However, this should have raised a question. Does NMP condense on cooler surfaces in such work as bathtub stripping? The incorrect modeling would suggest the potential for this to happen.

### Conclusions on the Exponential K1 Error.

The NMP modeling of air concentrations is seriously in error due to use of a completely inappropriate K1 value and this error must be corrected. The “downstream” calculations of MOEs etc. that use the incorrect MCCEM generated results must also be redone. It seems likely the DCM K1 was incorrectly used as the first order K1 for NMP, rather than the correct NMP K1 which must have resulted in the fit shown in Figure D-4 shown in item 1 of the attachments.

### Comments on Other NMP Modeling Issues

1. There appears to be a discrepancy on the vapor pressure of NMP. Table 2-1 page 17 and text on page 23 state the NMP vapor pressure as 0.19 mmHg at 25 C. This gives a saturated vapor concentration at 25 C of approximately 975 mg/M<sup>3</sup>. Other sources such as the manufacture’s MSDSs summarized in Table D-6, page 109 give the vapor pressure as 0.237 to 0.345 Torr all at 20C. Note the VP at 20 should be lower than at 25. What is the right value? Note 1 mm Hg is approximately 1 Torr.
2. Most (but not all) bathrooms have exhaust fans which if present would most probably be running during prudent stripping operations. Such fans are typically in the 50 to 110 CFM (1.4 to 3.1 M<sup>3</sup>/minute) but this does not seem to have been considered in the analyses.
3. The MRI chamber results merit additional discussion. As stated on page 91 of the draft NMP RA, **“The air exchange rate of approximately 0.5 ACH was intended to replicate the ventilation rate of an enclosed room in a typical residence as a worst-case scenario.”** Since a personal breathing zone sample was taken during the paint stripper use, the result should be a comparison point for all the scenarios evaluated with MCCEM. Page 92 of the NMP Draft RA states “In the MRI investigation, the only NMP-based paint stripper was brush applied. The breathing zone concentrations of NMP ranged from 37 to 39 mg/m<sup>3</sup> (9.1 to 9.6 ppm). The stationary length-of-task

concentrations ranged from 38 to 45 mg/m<sup>3</sup> (9.4 to 11.1 ppm). The 8-hour TWA concentrations ranged from 46 to 74 mg/m<sup>3</sup> (11.3 to 18.2 ppm).”

4. NMP Scenarios 1 to 8 evaluated with MCCEM use a double exponential model (Eq. D-5 page 96) with the two rate constants (K1 and K2) derived from fit to the MRI chamber data (EPA 1994b). Given good data from the MRI study, this gives an adequate basis for determining the rate of NMP emission to air, under reasonably similar conditions. However, NMP will have a reduced vaporization rate at low air velocities. One source to support this is Matthews 1989 cited in DCM RA for other reasons.

In industrial hygiene modeling, this has been called “back pressure” and especially for short duration activities with limited and low velocity airflow, a thin saturated vapor layer above the evaporating film suppresses further evaporation and saturation concentrations exist only very close to the film surface. This then disperses with the air flow, and the general space concentration rises, reaching a fraction of saturation that depends on the source NMP generation and dispersion, ventilation and volume. Failure to consider this may lead to significant overestimation of the NMP concentration in air. This may be handled better via different modeling equations than the ones used in MCCEM. A well-mixed (single chamber) equation that provides for this is given in Chapter 5 of Keil, C. B., Ed. (2000). *Mathematical Models for Estimating Occupational Exposure to Chemicals*. Fairfax, VA, AIHA Press. Other forms of the model exist, including in a freeware spreadsheet [IH Mod, available at:

<http://ss4m.aiha.org/insideraiha/volunteergroups/EASC/Pages/EASCTopics.aspx>.

While very difficult to determine without actual experimental data, the thin film stratification of NMP may be significant in a restricted space and a concave surface with limited effective air velocity over the surface, such as a bathtub. At low air velocities, there is little turbulence to drive dispersion. These considerations place significant doubt on the application of the MRI Ks for the bathtub stripping scenario. This could be verified with some simple laboratory scale experiments.



## ATTACHMENTS NMP Modeling Issues

- Figure D-5 and Table D-3 from page 101 of draft NMP Risk Assessment. These are stated as the results of fitting exponentials to the measured chamber concentration on the y axis. The Cmax is approximately 65 PPM or 263 mg/M<sup>3</sup> since 1 ppm = 4.06 mg/M<sup>3</sup>. These results CANNOT be as they are with a K1 of 10 per hour.

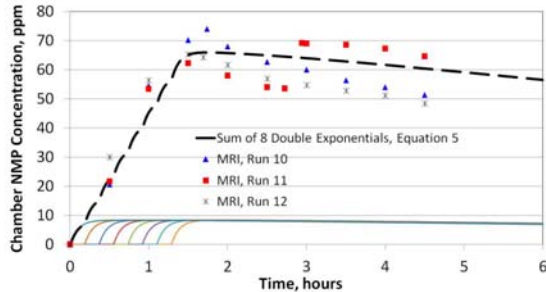


Figure D-5. Model Fit to MRI (US EPA, 1994b) Data for Wood Finisher's Pride (Brush Application).

Table D-3. Fitted Parameters to the US EPA (1994b) Study Results for Wood Finisher's Pride.

Product	Mass of Product Applied, g	NMP Mass Applied, g	1 <sup>st</sup> Exponential		2 <sup>nd</sup> Exponential	
			NMP Fraction Released	First-Order Rate Constant, Hour <sup>-1</sup>	NMP Fraction Released	First-Order Rate Constant, Hour <sup>-1</sup>
Wood Finisher's Pride	866	390	0.02	10	0.24	0.05

This first order rate constant (K1) of 10 per hour cannot be from the fit to the data in the graph above. **A K1 of around 0.3 per hour is consistent with the curve fit to the data.** See the results shown in Item 2 and 3 below.

- IH Mod Well Mixed Room Model with Exponentially Decreasing Emission Rate, attempt to replicate chamber results but **using INCORRECT first order decay constant for NMP of 10 per hour = 0.17 per minute.** Parameters for the NMP quantity and chamber conditions as given in US EPA (1994b). Consumer exposure to paint stripper solvents. US Environmental Protection Agency, Washington, DC, but converted to PER MINUTE. Note Cmax of 248 mg/m<sup>3</sup> at 20 minutes. Note this is a version of a predecessor to IH Mod. The revised spreadsheet considers the second exponential mass and second exponential constant of 0.05 per hour = 0.00083 per minute.

**The Well-Mixed Room Model with an Exponentially Decreasing Emission Rate**

If  $C_{in} = 0$  (no contaminant in the supply air), and  $k_L = 0$  (no loss mechanisms other than exhaust air)

$$C(t) = \frac{\alpha \cdot M_0}{\alpha \cdot V - Q} \left[ \exp\left(-\frac{Q}{V} \cdot t\right) - \exp(-\alpha \cdot t) \right] + C_0 \cdot \exp\left(-\frac{Q}{V} \cdot t\right) + \frac{\alpha_2 \cdot M_2}{\alpha_2 \cdot V - Q} \left[ \exp\left(-\frac{Q}{V} \cdot t\right) - \exp(-\alpha_2 \cdot t) \right] + C_0 \cdot \exp\left(-\frac{Q}{V} \cdot t\right)$$

$C(t)$  = vapor concentration (mg/m<sup>3</sup>) at time  $t$  (min)  
172.85 mg/m<sup>3</sup>

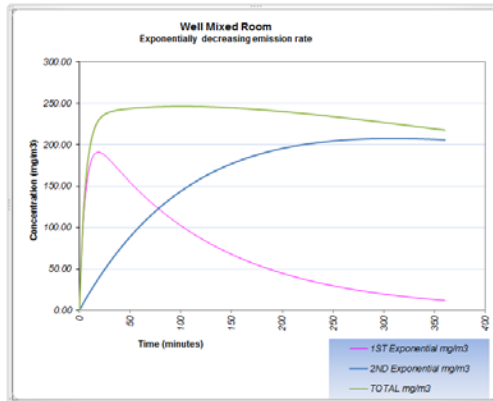
21.21

**INPUT VALUES 1st exponential**  
 7000 M0 = initial liquid mass (mg)  
 0.17 α = evaporation rate constant (min<sup>-1</sup>)  
 0.25 Q = room supply/exhaust air rate (m<sup>3</sup>/min)  
 0 C0 = vapor concentration at t = 0  
 25 V = room volume (m<sup>3</sup>)  
 10 t = time of interest (minutes)

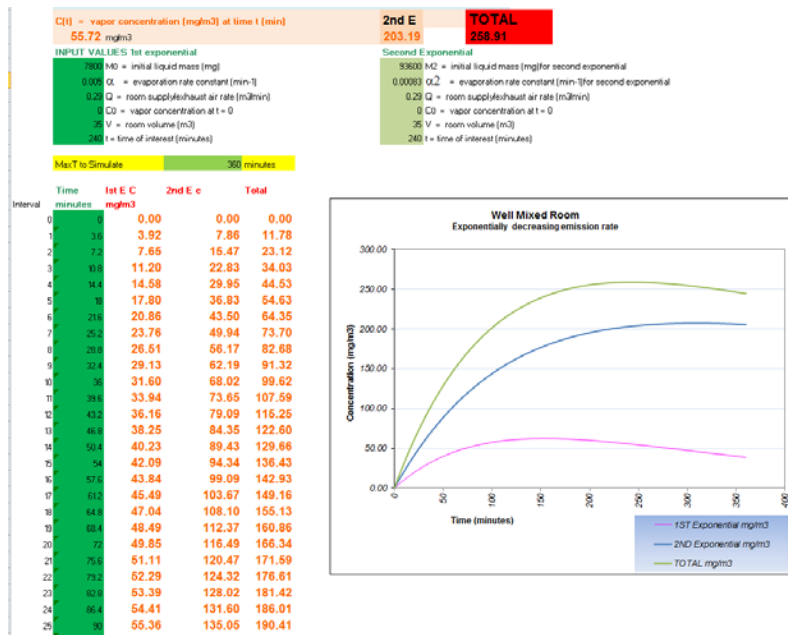
**Second Exponential**  
 93600 M2 = initial liquid mass (mg) for second exponential  
 0.00083 α2 = evaporation rate constant (min<sup>-1</sup>) for second exponential  
 0.25 Q = room supply/exhaust air rate (m<sup>3</sup>/min)  
 0 C0 = vapor concentration at t = 0  
 25 V = room volume (m<sup>3</sup>)  
 10 t = time of interest (minutes)

Max T to Simulate 300 minutes

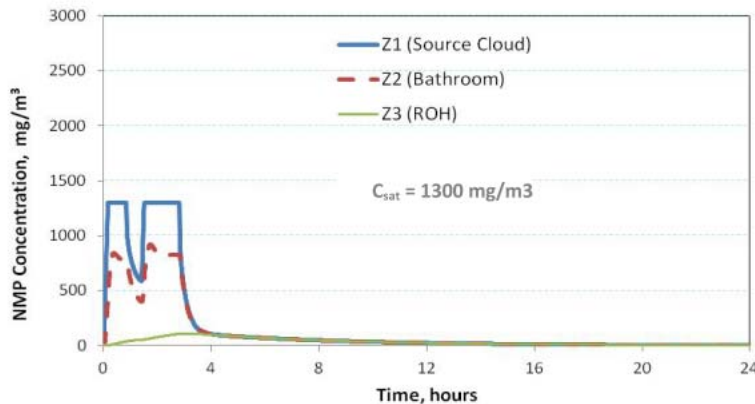
Time minutes	1st E c mg/m <sup>3</sup>	2nd E c	Total
0	0.00	0.00	0.00
1	100.35	7.86	108.21
2	151.82	15.47	167.29
3	176.87	22.83	199.69
4	187.67	29.95	217.62
5	190.83	36.83	227.67
6	189.93	43.50	233.42
7	186.90	49.94	236.84
8	182.79	56.17	238.96
9	178.17	62.19	240.36
10	173.34	68.02	241.36
11	168.46	73.65	242.11
12	163.63	79.09	242.73
13	158.89	84.35	243.24
14	154.26	89.43	243.69
15	149.74	94.34	244.09
16	145.35	99.09	244.44
17	141.08	103.67	244.76
18	136.94	108.10	245.04
19	132.92	112.37	245.29
20	129.01	116.49	245.51
21	125.22	120.47	245.70
22	121.54	124.32	245.86
23	117.97	128.02	246.00



- IH Mod Well Mixed Room Model with Exponentially Decreasing Emission Rate attempt to replicate chamber results using an **APPROPRIATE VALUE of the first order decay constant for NMP of 0.3 per hour = 0.005 per minute.** Parameters for the NMP quantity and chamber conditions as given in US EPA (1994b). Consumer exposure to paint stripper solvents. US Environmental Protection Agency, Washington, DC, but converted to PER MINUTE. Note this model does not consider the second order decay constant, leading to an underestimate particularly for later time intervals. However, the timing and value of the peak concentration are quite similar to the chamber results shown in the first figure above. Note the Cmax of 264 mg/m<sup>3</sup> is actually at about 240 minutes but the shape of the curve and peak concentration reasonably replicate data in Figure D-5 in Item 1 above. The time axis on the graph below is not correct. Note these results arise from a custom modified version of IH Mod that also considers the second exponential mass and second exponential constant of 0.05 per hour = 0.00083 per minute.

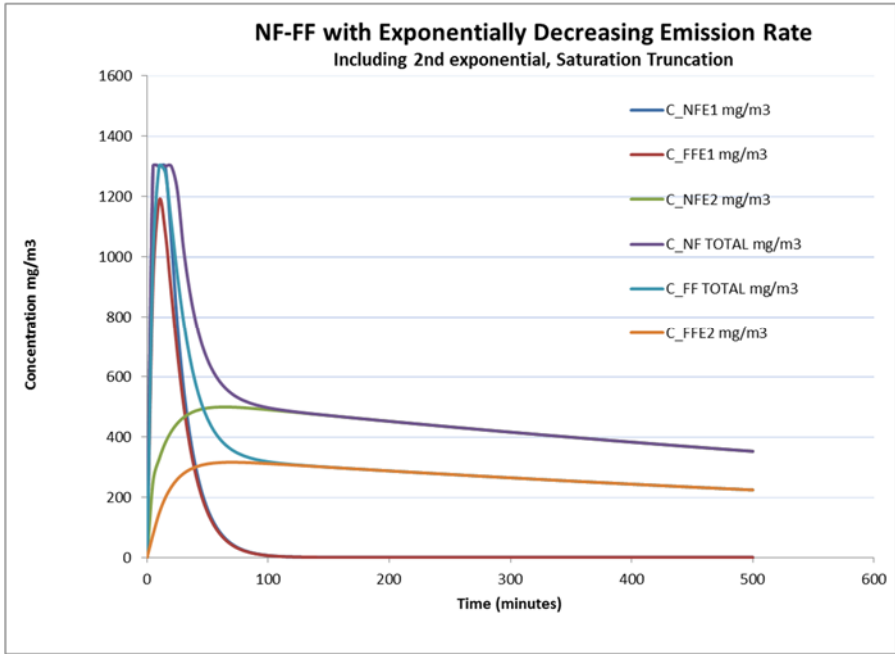


4. Scenario 7, Bathtub Refinishing. Copy of NMP Draft RA Bathtub Brush On NMP Stripper Scenario from P. 117, NMP Draft RA

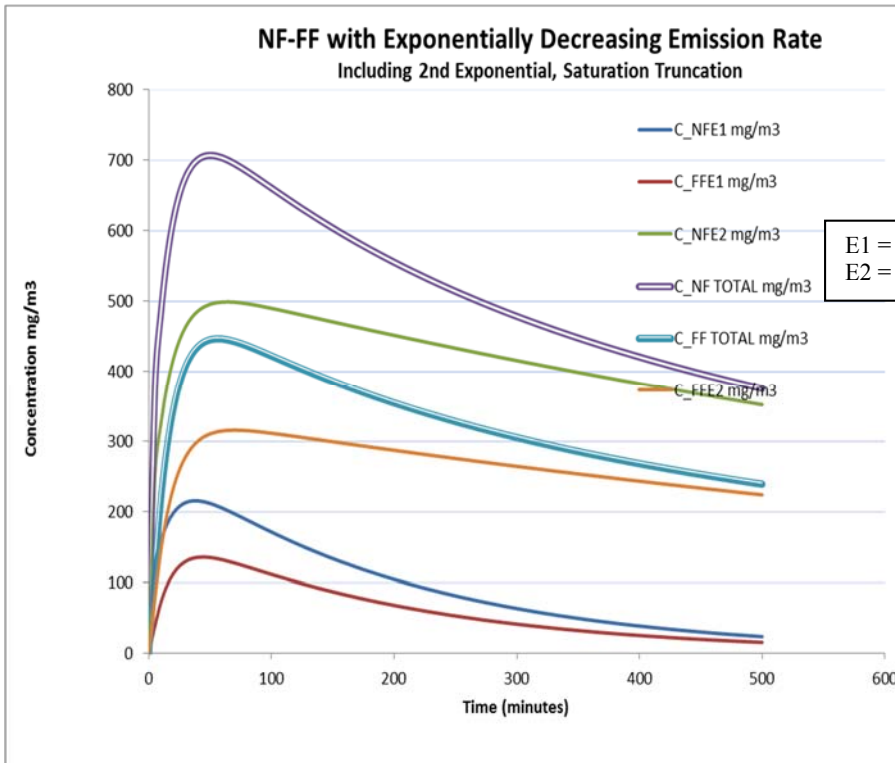


a) Scenario 7, Saturation Concentration Constraint at 1,300 mg/m<sup>3</sup>

5. Scenario 7. Near Field Far Field Model (Modified predecessor to IH Mod) using **INCORRECT K1 of 10 per hour**. Note: This graph was generated by truncation of concentration at saturation of 1300 mg/m<sup>3</sup>. Note the  $C_{max} = C_{max}$  of the MCCEM results. The  $C_{NF}$  Total is an estimate of the concentration in the source cloud. The  $C_{FF}$  Total is an estimate of the concentration within the bathroom. This model does not address the rest of the house.

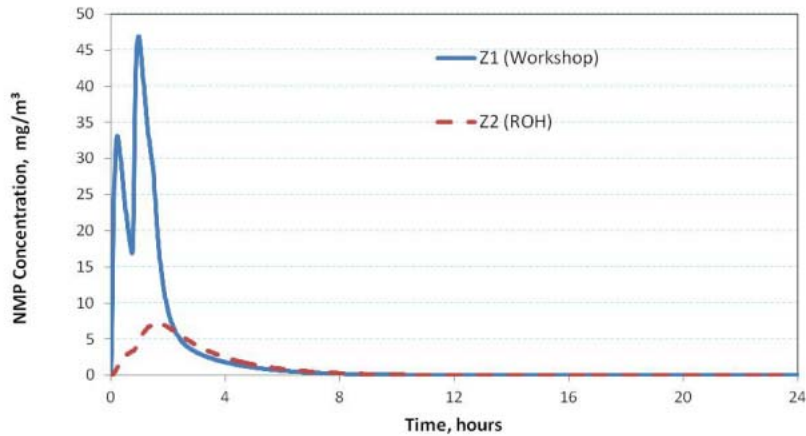


6. Scenario 7, Bathtub Refinishing. Near Field Far Field Model (IH Mod) **Using APPROPRIATE K1 of 0.3 per hour = 0.005 per minute.** Note the  $C_{max}$  of 706  $mg/m^3$  is not equal to the MCCEM results  $C_{max}$  of 1300  $mg/m^3$ , and the  $C$  vs.  $t$  curve is substantially different. The  $C_{NF}$  Total is an estimate of the concentration in the source cloud. The  $C_{FF}$  Total is an estimate of the concentration within the bathroom. This model does not address the rest of the house.



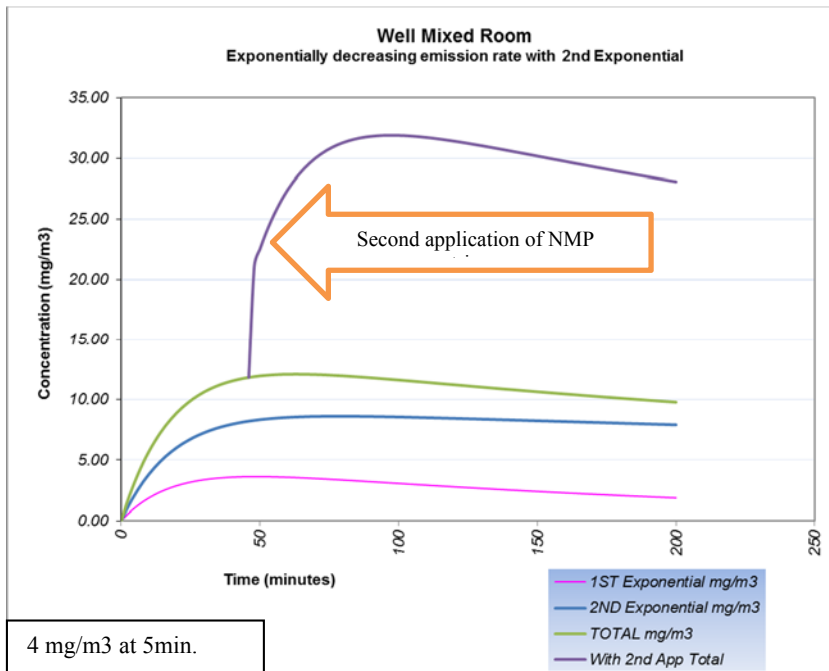
E1 = first exponential (K1)  
E2 = second exponential

7. Scenario 1 MCCEM Results NMP Daft RA p 114



a) Scenario 1, Brush Applied

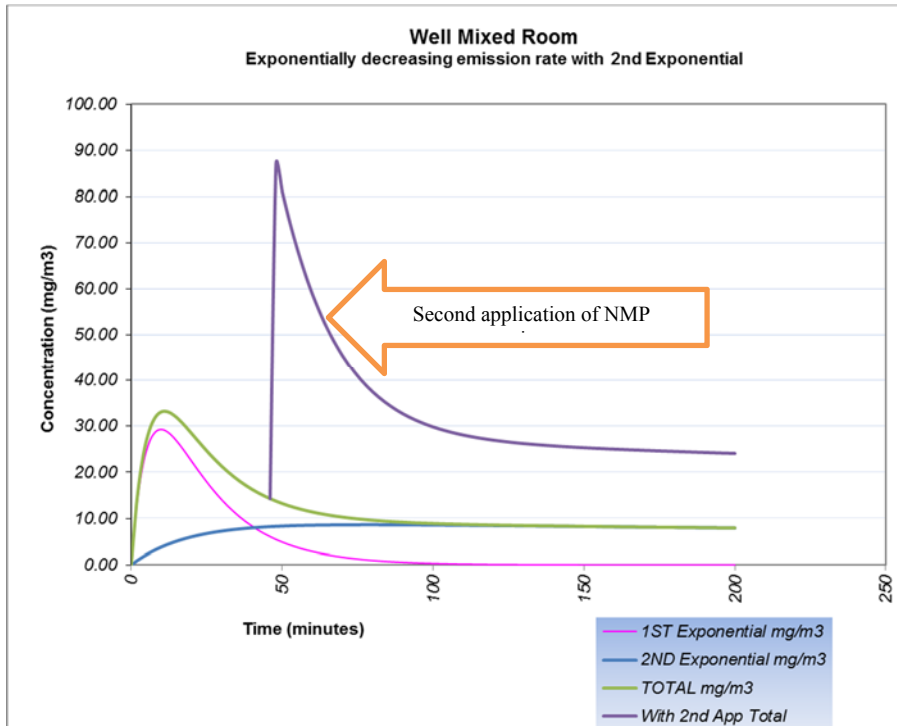
8. Scenario 1. Brush Applied NMP in a Work room. This graph does not consider the applicator moving in and out of the zone. Rather, this displays the concentration series in the work zone. This uses an appropriate first exponential K of 0.3 per hour and the second exponential K of 0.05 per hour. Note the peak concentration does not reach the peak concentrations in the Draft NMP Scenario results, C<sub>peak1</sub> application 1 of 33 mg/m<sup>3</sup> at 5 minutes or C<sub>peak2</sub> application 2 of 47 mg/m<sup>3</sup>. Note the time course is different, which will significantly alter the time averaged personal exposures.



4 mg/m<sup>3</sup> at 5min.

Approx. 25 mg/m<sup>3</sup> at 45 to 50 min Application 2. C<sub>peak</sub> is after the user exits the zone but is during the scraping phase.

9. Scenario 1, **using the INCORRECT first exponential (K1) of 10 per hour.** This does not quite replicate the Cmax of the MCCEM results for Scenario 1 for the second application. The first application peak replicates well. The second order exponential (K2) may not be quite correct and the ventilation in MCCEM is handled differently in the calculations.



## Anneclaire De Roos

### Document, Overall

There is a notable lack of epidemiologic study review included in the document, although I suspect that there has been very little epidemiologic research done specifically on health effects of NMP exposure.

Figures F-1 & F-2 are mislabeled as showing mg/m<sup>3</sup> (rather it should be ppm).

### Occupational Inhalation Exposure

The occupational inhalation exposure assessment included very few data sources, as noted in the draft risk assessment document. The studies listed in Table 3-3 should be individually listed, as it is difficult to refer back to the original studies based on the presentation, as is.

There are several studies & measured values listed in the text that are not included in Table 3-3.

The text describes an 8-hr TWA estimated in the EPA (1994) study of volunteers, of 46-74 mg/m<sup>3</sup> (11.3-18.2 ppm). This 8-hr TWA is higher than other concentrations listed in Table 3-3. During the phone meeting on 12/13/13, an EPA staff member explained that the 8-hour TWA from this study was not measured in a way that is suitable for comparison to the other 8-hour TWAs listed. While this explanation is acceptable for not including the TWA in Table 3-3, perhaps the value could be used as a data point in the risk assessment, with a goal of providing a range of MOEs for the occupational inhalation exposure setting (rather than the one MOE calculated for occupational exposure).

Several studies of “non-specified paint stripping” activities were found, as described in the text, but were not included in Table 3-3. The NMP air concentrations in one of these studies were higher than those in Table 3-3, with 1-hr peak exposure as high as 280 mg/m<sup>3</sup> (69 ppm) and an 8-hr TWA of 64 mg/m<sup>3</sup> (16ppm). During the phone meeting on 12/13/13, an EPA staff member confirmed that this study of “non-specified paint stripping” should in fact have been included in Table 3-3 (it was unintentionally left out). These levels should also be included in the risk assessment of occupational inhalation exposure, to provide a range of plausible MOEs.

With so few data sources available, a modeling approach similar to that used for the consumer user inhalation (MCCEM) might have been appropriate to estimate a range of exposures, particularly since parameters in small businesses (workshop room volume, air exchange) may be similar to residences. In fact, professional contractors probably often perform this type of paint stripping work for clients within private residences.

There is no mention of the EU 1999 report (TNO 1999) in the NMP risk assessment (it was mentioned in the methylene chloride document). This is relevant, as the EU report states that there is “probably no fundamental difference between the application of paint removers by professional painters and consumers”, and provides support for the fact that the sparse occupational inhalation exposure data could have been supplemented by a similar modeling approach as for consumers.

### **Consumer Inhalation Exposure**

It is a strength that the MCCEM approach allows estimation of a range of exposure for both the user and non-user in a residence, based on limited exposure measurement data. The scenarios chosen were generally reasonable to represent central tendency & upper-end user/non-user scenarios.

There is quite a bit of uncertainty in the data used in the models. The data were sometimes old or were for other chemicals (e.g., DCM data were used to fit the exponential for mass release to the spray scenario). Nevertheless, the values generated seem realistic for the user when compared to some of the occupational inhalation values. Occupational values listed are 13-39 mg/m<sup>3</sup> for professional contractors for task-based, short term or peak exposures (Table 3-3) and 280 mg/m<sup>3</sup> for non-specified paint stripping 1-hr peak exposure (Appendix). The consumer user values generated in the MCCEM approach (1-hr maximum for workshop scenarios) were 13, 65, 98, 34, 100, and 150. These values are comparable to those from the occupational studies (note that the graffiti remover workers are probably not comparable to the consumer users modeled here because they are likely working outdoors, unlike the residential user in their workshop). The residential user values in the bathroom setting (scenarios 7 & 8) are quite a bit higher (830 & 580

mg/m<sup>3</sup> for 1-hr max), but this is a unique setting that may not be comparable to the occupational studies. There are no known data with which to compare the *non-user* values from the MCCEM to a real-life setting.

The study used to develop the exponential model of chemical mass release (EPA 1994) is referred to as an occupational study on page 31 & page 43. This chamber study is not truly a study of an occupational setting, and in fact, it is referred to as a study of consumer exposures on page 91. It should be referred to as a chamber study in both the occupational and consumer inhalation exposure sections. I believe it is an appropriate study to use for either occupational or consumer exposure modeling.

An overarching comment that applies to the exposure models as well as the risk characterization is that inhalation exposure doesn't occur in isolation from dermal exposures. The combined exposure to inhalation and dermal should be addressed to estimate a total dose. The consumer user would have dermal exposures both from product splashing on their hands/arms/face (even if they are wearing gloves, as recommended) and from aerosolized exposure (particularly in the case of using spray-on product). This is a significant deficiency of the exposure modeling, and because of this, the modeled inhalation exposures wouldn't necessarily be reflective of the total potential dose.

There are some data values which seem less-than-realistic, as well as some additional scenarios that may be warranted:

- The application and scraping times seem unrealistically low for a central tendency scenario (5 min brush application, 10 min scraping for coffee table). These application/scraping rates are based on the EPA 1994 chamber study of exposure to paint strippers in which volunteers applied paint stripper to a plywood panel). Ash 1992 showed that time for application/wait/scrape is on average an hour, implying longer time spent with the product. Therefore, the values presented probably should not be called 'central tendency', as they are likely low. In addition, the rates based on the EPA 1994 chamber study do not account for an unpracticed consumer, possibly intricate woodwork, as well as organization/cleanup time in workshop (it is likely that even if the consumer leaves the workshop during the wait time, they probably don't leave immediately). These factors seem important to vary, particularly as the sensitivity analysis indicated that time spent in the workshop was an important determinant of exposure. A question for the EPA staff: Were the application/wait/scrape times included as parameters in the sensitivity analysis? If so, then it can at least be determined whether doubling/halving these values provides substantial influence on the overall results. This would be useful to know, as it may alleviate concern about these parameters. If the overall results are in fact sensitive to variation of these parameters, then perhaps doubling the application/scrape times could be used for upper-end scenarios, as there are no other known specific references for more realistic application/wait/scrape times.
- Only scenario 7 has closed windows (one of the bathroom scenarios). Although opening the window is recommended, there are data indicating that a substantial proportion of users do not open the window when using paint strippers. Riley 2001 found that 55 percent of users reported opening the window when using paint strippers. Earlier studies found higher percentages of users opened windows (upwards of 80%). In either case, however, there is evidence that a substantial proportion of users do not open the windows, and the consumer



user scenarios in the workshop should be varied to reflect this, particularly since the sensitivity analysis shows that the workshop ACH is a strong determinant of both user and non-user 24-hr TWA exposures.

- There is no spray-on scenario for the bathroom. Although these scenarios already represent upper-end scenarios, adding another scenario for use of a spray-on product in the bathroom should be considered.

Use of the term “application rate” for g/ft<sup>2</sup> is confusing. To me, rate implies the pace (amount per time frame), whereas this is the amount per surface area.

### **Dermal Exposure – Occupational & Consumer**

There are a number of very conservative assumptions made in this section, which is inconsistent with the rest of the document in which a mix of conservative and anti-conservative assumptions are used. Conservative assumptions are that workers do not wear protective gloves and assuming 100 weight percent NMP and maximal absorption through the skin. On the flip side, an anticonservative assumption is that there is only one exposure per day to the hands. One exposure per day is completely unrealistic given the apply/wait/scrape/repeat procedure used for most of the paint stripping products. Presentation of a range of scenarios (as in the consumer inhalation exposure modeling) would make the results easier to interpret and use in risk characterization.

The reasoning behind the film thickness assumption for occupational (laboratory tests) vs. consumer dermal exposures (expert judgment) is not clear.

Dermal exposure should be estimated separately for women, using female-specific body weight and hand size. This is essential since the main identified hazard for NMP is developmental toxicity during gestation.

### **Hazard Identification & Dose Response Assessment**

Use of a developmental toxicity endpoint is appropriate, as no other effects were observed (although this doesn't prove that other effects don't exist). I believe it appropriate to use an acute POD based on fetal body weight decrements that were observed in the presence of maternal body weight decrements, because this mechanism of fetal effect (through maternal weight loss) is plausible for humans.

The maternal NOAEL for weight loss should be analyzed in the MOE calculations along with the fetal body weight decrements – not because I believe that maternal weight loss by itself is a relevant toxicity endpoint, but because there is a trend of decreasing fetal body weight at each decrement in maternal body weight (even where the decreasing fetal body weight is not statistically significant for that category, there is a dose-response trend across the categories).

The general presentation in this section is very confusing. The subheadings separate out acute, subchronic, and chronic exposure studies; however, it would be helpful for the reader if the rationale was presented up front for using acute exposure studies for chronic dose-response and

for using chronic/subchronic exposure studies for acute dose-response. I agree with the approach, but stating that approach up front would guide the reader.

One concern is in regards to the use of a human body weight of 80 kg for conversion of the rat NOAEL to a human equivalent dose. This is greater than average for women, even during much of pregnancy. Since the main toxicological endpoint of concern is relevant for exposed women, female-specific exposure dose conversions and risk calculations should be made.

### **Risk Assessment**

Conclusions for risk evaluation of non-cancer chronic inhalation exposures to workers (“negligible risks of concern for workers” from MOEs on page 57) appear to be based solely on exposure levels for graffiti removers. This is an unacceptable conclusion since graffiti removers probably work outdoors and thus are likely to have lower inhalation exposures than indoor workers. The document in fact says that there was no other 8-hr TWA available for occupational inhalation values (page 57). However, the text describes an 8-hr TWA estimated in the EPA (1994) study of volunteers of 46-74 mg/m<sup>3</sup> (11.3-18.2 ppm) (page 92) and another 8-hr TWA of “non-specified paint stripping” activities of 64 mg/m<sup>3</sup> (16ppm) (page 92). Both of these are considerably higher than the TWA for graffiti removers, and even if none of these settings is broadly representative of workplaces, there should be multiple MOEs calculated for these different TWAs in order to represent a more realistic range of risk.

Assuming 24 hours/day exposure for occupational inhalation exposure is exceedingly conservative and not realistic. Or is this simply scaling? It’s not clear.

The conclusion on page 64 for consumer inhalation exposures is a bit misleading. It says that “Consumers may have potential risks of concern from inhalation exposure if exposed for more than 4 hours at lower ventilation rates.” This is misleading because a) MOEs were not calculated for <4 hours inhalation exposure, so it should be made clear that this doesn’t imply that shorter duration exposures are safe; and b) It’s a bit ambiguous to say the risk is “at lower ventilation rates.” The MOE for scenario 4 (spray application, central tendency scenario) was <30 and this was at the higher ventilation rate modeled. Scenario 2 also had an MOE <30 for the user, and was at the higher ventilation rate. Furthermore, every scenario except 7 & 8 assumed open windows (relatively good ventilation), whereas there is evidence suggesting that a substantial proportion of users do not open the windows when using paint strippers (Riley 2001). So, the message should not be that risk occurs at lower ventilation rates, since that implies that risk is only at low ventilation rates.

### **Dale Hattis**

OPPT focused its risk assessment on the use of NMP in paint stripping. There are human health concerns for developmental effects related to NMP use-application. Both inhalation and dermal exposures were evaluated and risk estimates were calculated for consumers and workers using NMP-based paint strippers. Risks also were estimated for individuals physically near the residential user, but not using the NMP-based product (also referred to as bystanders or non-users).

## **General Question on the Risk Assessment Document**

**Issue 1.** This risk assessment is divided into three chapters with seven appendices. Chapter 1 describes the scope for the NMP human health risk assessment. Chapter 2 provides information on chemistry, environmental fate and transport, production, and uses. Chapter 3 characterizes exposure, hazard, and risk findings as well as the uncertainties of the assessment. Supporting information is provided in the appendices. The risk assessment is intended to provide a clear and transparent summary of the Agency's analysis.

**Question 1-1:** Please comment on whether the risk assessment provides a clear and logical summary of EPA's analysis. Please provide specific suggestions for improving the clarity and transparency of the risk assessment document.

**There are numerous small errors and other anomalies that mar the document in its current form. These include:**

**pp. 44-46:**

**Statement that dermal exposure is “( $\leq 100$  %) depending on conditions” is not very informative. The contrast with the 40-60 percent range given for inhalation exposures seems to imply that dermal is more efficient than inhalation exposure in leading to absorption. This implication should be removed.**

**p. 46:**

**Repetition of the meaningless comparison given earlier, “NMP is well absorbed following dermal ( $< 100$  percent) and inhalation (40 to 60 percent) exposures.”**

**p. 151:**

**Caption to Figure F2 refers to data in Table D-1 when it should be F-1**

**pp.152-3 Captions in the figures refer to dose in  $\text{mg}/\text{m}^3$  but dose is actually stated in ppm**

**The plots show results of exponential models 2 and 3, but the AICs for the Hill and linear models are both listed as lower than these in Table F-2**

**The BMCL for the Hill model, with the lowest AIC is listed as 130.19—much less than the 300-odd  $\text{mg}/\text{m}^3$  shown for the linear and exponential models 2 and 3 that appear to have been chosen as the basis of the BMD determination**

**Question 1-2:** Please comment on whether appropriate background information is provided and accurately characterized. Please provide any other relevant literature, reports, or data that would be useful to support the risk assessment.

**I have previously provided the following additional citations that do not appear in the reference section of the document and may be helpful for the analysis:**

Meier S, Schindler BK, Koslitz S, Koch HM, Weiss T, Kafferlein HU, Bruning T (2013) Biomonitoring of exposure to N-methyl-2-pyrrolidone in workers of the automobile industry. *Ann Occup Hyg* 57:766-773.

Mohammed D, Matts PJ, Hadgraft J, Lane ME (2013) In Vitro-In Vivo Correlation in Skin Permeation. *Pharm Res*.

**An additional reference on skin absorption is used later in this review in checking EPAs skin absorption assumptions:**

Keener SA, Wrbitzky R, Bader M (2007) Human volunteer study on the influence of exposure duration and dilution of dermally applied N-methyl-2-pyrrolidone (NMP) on the urinary elimination of NMP metabolites. *Int Arch Occup Environ Health* 80:327-334.

### **Questions on the Exposure Assessment**

#### ***--Inhalation Exposures***

**Issue 2. EPA found limited published data for NMP's air concentrations in workplace settings during use of NMP-based paint strippers. These data were used for estimating occupational inhalation exposures to NMP in adult workers (e.g., male and female workers of childbearing age).**

**Question 2-1:** Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of the workplace inhalation exposure, including specific citations (if available) of data sources characterizing occupational inhalation exposures.

**The approach taken seems reasonable. However I think some more formal Monte Carlo/distributional treatment of uncertainty and variability in the modeling would have improved the analysis.**

**Issue 3. EPA conducted a literature review and found insufficient data to characterize inhalation exposures for residential users (e.g., adult users including women of childbearing age) and bystanders/non-users (i.e., children, women of childbearing age). Therefore, EPA used a modeling approach to estimate inhalation exposures. EPA found limited data on consumer uses and profiles and conducted a sensitivity analysis of model parameters to identify critical parameters essential to the inhalation modeling approach. EPA varied the most sensitive input parameters to generate central tendency and upper-end NMP air concentrations.**

**Question 3-1:** Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of consumer inhalation exposure, including specific citations of data sources characterizing consumer emission profiles of NMP-based paint strippers. As part of the review, please also evaluate the sensitivity analysis conducted for the assessment and comment on the strengths and weaknesses of the evaluation of different exposure scenarios and the choice of assumptions/input parameters for generating central tendency and upper-end NMP air concentrations.

*Dermal Exposures*

It seems important to me to check the dermal exposure model results with other data:

- **First, by checking the compatibility of the EPA model conclusions and assumptions with the uncited observations of (Keener et al., 2007) which give observations of dermal absorption based on 30-120 minute studies in live people to both 100 percent NMP and 50 percent NMP in water. Undiluted NMP was absorbed at a rate of about 6 mg NMP/(cm<sup>2</sup>-hr). 50 percent NMP gave rise to an absorption of less than this—0.9 mg NMP/(cm<sup>2</sup>-hr).**

EPA’s model assumptions are given on p. 26 in Table 3.2.

Dermal absorption model prediction	
surface density of film	0.7
Total NMP on hands	588
Area of hands exposed	840
Body weight (kg)	80
Modeled absorption	7.4
	592
Volume to contain this amount (mL)	0.57

Therefore, as indicated in the discussion, the EPA model essentially assumes 100 percent absorption of material on the hands, surely a worst case.

At Keener's observed dermal absorption rate of about 6 840 cm<sup>2</sup> of exposed area could deliver a maximum of 5040 mg per hour, therefore the model is compatible with this Keener observations.

**Issue 4. No data were found for occupational or consumer dermal exposures to NMP-based paint strippers. Thus, modeling approaches were used to estimate potential dermal exposures of adult users in contact with liquid NMP-based paint strippers at workplace and residential settings. The occupational and consumer dermal exposure estimates use similar “thin-film” modeling approaches. A primary difference between the approaches is the film thickness assumption. The estimates for occupational exposures are based on a range of film thickness values from laboratory tests of surrogate film materials. The film thickness value for consumer exposures was based on the professional judgment of a chemist employed in a paint stripping company.**

**Question 4-1:** Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of the workplace dermal exposure, including specific citations (if available) of data sources characterizing occupational dermal exposures. Please comment on the strengths and weaknesses of the evaluation and the choice of assumptions/input parameters for generating estimates of the NMP's dermal exposure.

**The basic approach seems reasonable. However I think the analysis would be improved by a more formal set of distributional representations of variability and uncertainty.**

**Question 4-2:** Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of the consumer dermal exposure, including specific citations (if available) of data sources characterizing dermal exposures in a residential setting. As part of the review, please comment on the strengths and weaknesses of the evaluation and the choice of assumptions/input parameters for generating estimates of the NMP's dermal exposure.

**The basic approach seems reasonable. However I think the analysis would be improved by a more formal set of distributional representations of variability and uncertainty.**

**Question 4-3:** Please comment on the assumptions used by the Agency regarding film thickness for the assessment, including any additional data on film thickness with which to assess dermal exposure to NMP for both consumers and workers.

**I do not have a good basis to evaluate this.**

## Questions on the Hazard Assessment

**Issue 5. EPA chose a point of departure (POD) from developmental inhalation studies in rats reported by Saillenfait et al. (2001, 2003)<sup>1</sup> to assess the acute inhalation scenario. It was assumed that a single exposure to NMP could be sufficient to produce adverse developmental effects (US EPA, 1991; van Raaij et al., 2003)<sup>2</sup>. From the Saillenfait studies, EPA chose a POD based on fetal body weight decrements to represent the effects of single acute inhalation exposure.**

1. Saillenfait, A. M., Gallissot, F., Langonne, I., Sabate, J. P., and Morel, G. (2001). Developmental toxicity of N-methyl-2-pyrrolidone administered by gavage or inhalation to rats. Poster presented at the 29th Conference of the European Teratology Society, 2-5 Sep 2001 Balatonfüred, Hungary.

Saillenfait, A. M., Gallissot, F., and Morel, G. (2003). Developmental toxicity of N-methyl-2-pyrrolidone in rats following inhalation exposure. *Food Chem. Toxicol.* 41(4), 583-588.

2. US EPA (1991). Guidelines for Developmental Toxicity Risk Assessment. EPA/600/FR-91/00. <http://www.epa.gov/raf/publications/pdfs/DEVTOX.PDF>

van Raaij et al. (2003). The relevance of developmental toxicity endpoints for acute limit setting. RIVM report 601900004.

[http://www.rivm.nl/dsresource?objectid=rivmp:16116&type=org&disposition=inline&ns\\_nc=1](http://www.rivm.nl/dsresource?objectid=rivmp:16116&type=org&disposition=inline&ns_nc=1)

**Question 5-1:** Please comment on EPA's use of the identified developmental studies and POD to assess acute inhalation exposures to NMP use in paint strippers. As part of the review, provide your input on the appropriateness of using an acute POD based on fetal body weight decrements that were observed in the presence of maternal body weight decrements following exposure to NMP during gestational days 6 to 13. Please comment on whether the maternal no-observed-adverse-effect level (NOAEL) of 122 mg/m<sup>3</sup> (Saillenfait et al. 2001, 2003) should be analyzed in the MOE calculations along with the fetal body weight decrements. Please specify any other endpoints that should be considered for the hazard evaluation of acute inhalation exposures. Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.

**In my judgment, although it is true that a single exposure could result in a fetal body weight decrement it is more likely that a general nonspecific toxicant such as NMP acts as a kind of tax on the resources that the developing pup (or baby) has available to grow and develop, resulting in an impaired weight during pregnancy and at birth. Thus I would express dose as an integrated average of the delivered dose/day over the period of gestation, with scaling to humans according to the BW<sup>3/4</sup> rule as done in the EPA analysis, absent a fully developed PBPK model to re-express the dose in terms of systemic AUC of the NMP parent.**

**In general I do not think that NOAEL findings should be used, as indicated in the question, in preference to benchmark dose results. However I do have difficulties with the benchmark dose analysis results reported in Appendix F-2. First, I think that a 5 percent relative fetal weight loss is too large to be used as a point of departure that represents anything like a tolerable degree of change in a parameter analogous to birth weight in people. In people direct cigarette smoking causes about a 6 percent change in birth weight and is associated with an important increase in infant mortality—so this degree of impairment of fetal growth/development is much larger than can be considered harmless. Second, the Hill model results shown in the first line of Table F-2 show an AIC which is much lower (better) than the two exponential models (2 and 3) evidently selected to provide the bottom line guidance on the BMC and BMCLs and featured in the presentation of fit results in Figures F-1 and F-2. I don't understand this choice.**

**Some additional light on the choice is provided in a document I have subsequently received entitled “Using Internal Dose-Response Comparisons to Identify Dose Metrics--Which Best Correlate With Toxicity” dated 9/16/13”. This document shows in Table 7 a Benchmark Dose Analysis of Combined Becci et al. (1982) and Sallenfait et al. (2003) for incomplete ossification in which the models showing the lowest AIC values are not chosen because there was more than a threefold difference between the modeled BMD and the BMDL. In the case of Table F-2, the Hill model with the lowest AIC does in fact have a nearly fivefold difference between the BMD and the BMDL. I think to reject models that describe the data well but have a large difference between BMD and BMDL is arbitrary and, if it is a new general practice at EPA, should be reconsidered.**

**Issue 6. EPA also chose to use the developmental inhalation studies in rats reported by Sallenfait et al. (2001, 2003) to evaluate the chronic occupational inhalation exposures. It was assumed that the repeated nature of exposure to NMP during pregnancy could produce adverse developmental effects. From these studies, EPA chose a POD based on decrements in fetal body weight to represent the effects of chronic inhalation exposure.**

**Question 6-1:** Please comment on EPA's use of the identified developmental studies and POD to assess chronic inhalation exposures. As part of the review, please comment on the appropriateness of using a developmental toxicity endpoint and the identified effects to assess chronic inhalation exposures to NMP-based paint strippers. Please specify any other toxicological endpoints that should be considered for the hazard evaluation of acute inhalation exposures. Also, please provide relevant data or documentation and rationale for including other studies and endpoints for consideration. 4

**I think the choice of study for benchmark dose analysis is appropriate.**



**Issue 7. EPA chose a developmental dermal study in rats to characterize acute and chronic hazard for the dermal exposure scenario. The POD was based on fetal body weight and fetal death to represent the effects of acute and chronic dermal exposure.**

**Question 7-1:** Please comment on EPA's use of the identified developmental study and POD to assess acute and chronic dermal exposures. As part of the review, provide your input on the appropriateness of using a developmental toxicity endpoint and the identified effects to assess acute and chronic dermal exposures to NMP-based strippers. Please specify any other endpoints that should be considered for the hazard of acute or chronic dermal exposures. Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.

**As indicated in my response to Issues 6 and 7 above I think it is appropriate to use the fetal weight reduction endpoint as the focus of BMD analysis for both inhalation and dermal exposure scenarios.**

**Issue 8. EPA evaluated whether a physiologically-based pharmacokinetic (PBPK) model could be used in the NMP workplan risk assessment. Poet et al. (2010) constructed a PBPK model to describe the toxicokinetics of NMP in pregnant rats and humans after oral, dermal and inhalation exposures to NMP. The authors used PBPK and benchmark dose (BMD) methodologies to estimate human equivalent concentrations/doses (HEC/HED) based on a POD for fetal body weight. EPA evaluated the model during the development of the draft NMP risk assessment, but did not use the original model due to uncertainties in the model parameterization. The authors have recently revised the model and submitted it to EPA for further consideration. EPA has reviewed the revised PBPK model and determined that it is appropriate for risk assessment purposes. A copy of the model evaluation report and the model files (including the code) has been posted in the NMP docket. EPA intends to use the revised model to evaluate the risks of acute and chronic inhalation and dermal exposures to NMP-based paint strippers.**

**Question 8-1:** Please review the model and comment on the Poet et al. (2010) analysis as well as EPA's evaluation of the revised model. Please comment on whether the model is clearly and transparently described and technically and scientifically adequate for supporting OPPT's workplan risk assessment for NMP-based paint strippers. Specifically, please address the structure of the PBPK model, parameter calibration and model predictions of the available *in vivo* data.

**I evaluated the Poet et al. description of the model.\* The review of the material I have recently received does not change my observations as indicated below.**

**I have reviewed the published paper reporting the model in some detail:**

Poet, T. S., Kirman, C. R., Bader, M., van Thriel, C., Gargas, M. L., and Hinderliter, P. M. (2010). Quantitative risk analysis for N-methyl pyrrolidone using physiologically based pharmacokinetic and benchmark dose modeling. *Toxicol. Sci.* 113(2), 468-482.

**One result that is particularly important to review carefully is the unusual apparent finding of greater internal dose per unit mg/kg external dose in rats than in humans. This is the opposite of what is usually found, as humans, with larger body weights and slower metabolism/body weight tend to metabolize chemicals more slowly than rodents. The usual result, based on the Body Weight<sup>(3/4)</sup> metabolic scaling rule is that humans eliminate chemicals with about a 4-fold longer rate constant than rats.**

**For PBPK models, a key set of parameters affecting the internal predicted doses are those determining the rates of metabolism in different species—the maximum velocity (V<sub>max</sub>) and the substrate concentration ([C]) at which half of the maximum velocity is reached (K<sub>m</sub>), as specified in a Michaelis-Menten equation for the reaction rate:**

$$\text{Reaction rate} = \frac{V_{\max} * [C]}{K_m + [C]}$$

**In the case of the NMP models the reaction rate of most interest is a rate of detoxification of the parent NMP to putatively inactive metabolites (initially, 5-HNMP) that are later excreted. Other things being equal, faster the reaction rate, the lower the internal dose X time product that will result from a given amount of NMP absorbed.**

**The Poet et al. paper gives the following description of their use of metabolism data as inputs to the calibration of their model:**

**“The metabolism of NMP has been measured *in vivo* and *in vitro* in the rat (Payan et al. 2002) and in human microsomes (Ligocka et al. 2003). These rate constants were**

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**\* I have just recently received a report by a contractor and a preface by an EPA researcher evaluating the newly revised model that EPA evidently has decided to use. (Schlosser, P. “Preface to “A PBPK Model Quality Assurance Assessment for the TSCA Workplan Risk Assessment of N-Methylpyrrolidone”; and the accompanying contractor’s report,--Lumpkin, MH, Gentry, PR, “A PK/PBPK Quality Assurance Assessment for the TSCA Workplan Risk Assessment of N-Methylpyrrolidone.” Combined document apparently dated 9/16/13). This document in turn refers to “Simulations of rat and human exposures that were presented by Poet (2013). This new reference is “Poet. (2013). Internal Dose, as Derived from Updated PBPK Model, Should Be Basis for NMP Toxicity Assessment. Battelle Memorial Institute Pacific Northwest Division.” I do not yet have this new Poet report. My review of the contractor report indicates that the model code now seems to work and reproduce the published results. There is no change to the basic metabolism constants or the model structure originally described by Poet et al. (2010). The rest of the response to this question represents my earlier findings from the original Poet et al. paper and the indicated consequences for comparative dosimetry in rats and people. Additional notes on the document are provided as an appendix at the end of this set of responses.**

converted to units utilized by the model ( $\text{mg/h/kg}^{0.75}$ ) and used as initial parameters. In order to extrapolate from *in vitro* data to an *in vivo* metabolism rate, protein yields and original liver and body weights were needed but not available, so historical values from our laboratory were used. The maximal rate of metabolism ( $V_{\text{max}}$ ) used for rats was 50 percent of the estimates from the *in vitro* rates from Payan et al. (2002) and approximately two times the estimated rates extrapolated from Ligoicka et al. (2003) for humans.”

It is likely that the combined effect of the two-fold downward adjustment of the rat metabolism rates and the two-fold upward adjustment of the human metabolism rates would be to produce approximately a four-fold lower expected human internal dose relative to the rat internal dose for comparable NMP intakes per body weight compared to a case where the measured rat and human *in vitro* rates were used unchanged. Thus in evaluating the PBPK models’ dosimetry findings it is crucial to evaluate whether these adjustments were appropriate.

In doing this, it should be understood that *in vitro* measurements in microsome systems are not infallible predictors of the rates at which metabolic enzymes will operate *in vivo*. Microsome measurements are often made under conditions of pH and cofactor concentrations that maximize activity in order to minimize experimental variability and to make the measurements as easily distinguished as possible from whatever background noise may be present in the system. In addition, although the usual convention of PBPK modeling is to place all the metabolism in the liver, other organs are also metabolically active, albeit at lesser rates per gram of tissue.

The final metabolism values are listed by Poet et al. as having been the result of an optimization process. This must be based on some other empirical data, ideally collected from *in vivo* observations, such as blood levels or, at minimum, urinary excretion rates of metabolites. My focus in this review is therefore on doing at least an initial check of the plasma AUC predictions in humans against whatever empirical data are available. Later in the Poet paper (p. 473) it is reported that “The adult human PBPK model was calibrated with data from Bader and van Thriel (2006 and reported herein) and Bader et al. (2008).<sup>1</sup>

These references are:

Bader, M. and van Thriel, C. (2006) Human volunteer study on biomarkers of N-methyl-2-pyrrolidone (NMP) after inhalation exposure. Report for the NMP producers group, Washington, DC.

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<sup>1</sup> The human volunteer study reported is based on exposures of “eight healthy nonsmoking male (emphasis added) volunteers (mean age: 26 years, range 23-29 years),... exposed whole body in groups of four to NMP vapor concentrations of 10 mg/m<sup>3</sup> (measured average  $9.7 \pm 0.8$  mg/m<sup>3</sup>), 40 mg/m<sup>3</sup> (measured average  $40.3 \pm 1.0$  mg/m<sup>3</sup> and 80 mg/m<sup>3</sup> (measured average  $80.0 \pm 1.6$  mg/m<sup>3</sup>... Each group was exposed for 6 h and 10 min with an exposure-free interval of 10 min for collection of blood samples outside the exposure chamber. The three NMP concentrations were presented in ascending order, and an exposure-free period of 1 week between subsequent sessions was strictly adhered to.”

Bader, M., Wrbitsky, R., Blaskewicz, M., and van Thriel, C. (2008) Human volunteer study on the inhalational and dermal absorption of N-methyl-2-pyrrolidone (NMP) from the vapour phase. *Arch Toxicol* 82:13-20.

**I have now evaluated some data in the other cited papers providing human NMP blood or plasma levels. I think it is important to focus on these measurements, rather than the detailed urinary excretion observations that were also included in the Poet calibrations, because the plasma NMP is the key dosimeter for relating human internal doses to the rat internal doses.**

**In the Bader and Van Thriel study, eight young male subjects were given 6-hour exposures to NMP in a series of 3 ascending concentrations (averaging 9.67, 40.25, and 80 mg/m<sup>3</sup>). A week was allowed between these exposures. The Bader and van Thriel report contains plasma NMP concentration data from blood samples taken just before, and at 7 subsequent time points ranging from about 3 hours through 48 hours after the start. I used these data to directly calculate simple AUCs (Area Under the Concentration X time curve) for the intervals between each sampling time point for each subject for each exposure. Implicitly this was done by drawing straight lines between the adjacent time points and summing up all the AUC for each interval. The summary results of these calculations are given in Table 1 on the next page. The first three numerical columns give the AUCs for the three exposure levels in µg-hr/liter. The next three numerical columns show the results of dividing these AUC results by the product of the exposure level and duration). If there were no nonlinearities, the first three values should increase in direct proportion to the exposure level, and the second three values should be more or less constant.**

**As it happens this is not so, and not so in an interesting and unusual way. As can be seen in the footnotes at the bottom of the table, the differences between the AUC/(exposure level \* time) ratio for the lowest exposure level are significantly different from the analogous ratios at the two highest exposure levels. This is just the opposite of what one would expect for simple saturation of metabolic detoxification of NMP. For saturation of detoxification, the AUC/external concentration X time should rise, not fall with increasing exposure levels. Possible mechanisms that could produce this include an induction of metabolism at higher exposure levels or (less plausibly) a saturation of an uptake process. Whatever the mechanism, it seems to me that the PBPK model should be adapted to reflect this clear tendency in this set of calibrating data. Absent this, it is likely that the current PBPK model, calibrated to produce a “best fit” to the data at all three doses will tend to make predictions for larger metabolism rates and lower internal AUC doses for humans than would be expected at lower exposure levels.**

**The issue arises, how this apparent saturation of metabolism should be represented mathematically. I think the first choice for this would be to assume that the metabolism rate rises according to a Michaelis-menten like saturation formula.**

**Metabolism rate with induction (Vmax for NMP loss) =**

$$V_{\max \text{ lowdose}} * \frac{\text{Maxinduction\_level} * [C]}{Q + [C]}$$

**Table 1****Analysis of Plasma NMP AUCs and AUCs/(exposure level \* time) From the Unpublished Report of the Bader and Van Thiel Study of Eight Human Subjects Exposed to NMP via Air**

Parameter	AUC			AUC/hr*		
	AUC (µg- hr/liter)	(µg- hr/liter)	(µg- hr/liter)	mg/m <sup>3</sup>	mg/m <sup>3</sup>	AUC/hr*mg /m <sup>3</sup>
Exposure Level (6 hrs) mg/m <sup>3</sup>	9.67	40.25	80	9.67	40.25	80
Participant 01	5513	9224	13308	95.0	38.2	27.7
Participant 04	6235	9183	13176	107.5	38.0	11.6
Participant 10	4675	5856	10926	80.6	24.2	22.8
Participant 12	1329	4751	9381	22.9	19.7	19.5
Participant 14	1383	5015	14298	23.8	20.8	29.8
Participant 16	1587	6407	18106	27.4	26.5	15.9
Participant 17	3122	4666	21821	53.8	19.3	45.5
Participant 25	3288	6111	16160	56.7	25.3	14.2
Amean, All Participants	3391	6401	14647	58.4	26.5 <sup>a</sup>	23.4 <sup>b</sup>
SD, All Participants	1922	1842	3989	33.1	7.6	11.0
Std Error	680	651	1410	11.7	2.7	3.9
Gmean, All Participants	2886	6191	14186	49.7	25.6 <sup>c</sup>	21.4 <sup>d</sup>
GSD	1.876	1.311	1.310	1.876	1.311	1.562
log(GSD)	0.273	0.118	0.117	0.273	0.118	0.194

<sup>a</sup> P < 0.02 by T test for the difference with the 9.67 mg/m<sup>3</sup> exposure rate, assuming equal variances; P < 0.03 assuming unequal variances.

<sup>b</sup> P = 0.013 by T test for the difference with the 9.67 mg/m<sup>3</sup> exposure rate, assuming equal variances; P = 0.02 assuming unequal variances.

<sup>c</sup> P = .016 by T test for the difference with the 9.67 mg/m<sup>3</sup> exposure rate, assuming equal variances; P < 0.02 assuming unequal variances, based on the means of the log values.

<sup>d</sup> P < .01 by T test for the difference with the 9.67 mg/m<sup>3</sup> exposure rate, assuming either equal or unequal variances, based on the means of the log values.

However a remaining difficulty is that this ignores the issue of the dynamics of induction and the dynamics of the reversal of induction after induction has occurred. I suspect that the available human data may not be sufficient to determine this unambiguously, but some attempt might be made perhaps using other data in the drug literature that may be informative on the dynamics of P450 metabolism induction in humans.

Table 1 also shows results of evaluations of the human interindividual variability in AUCs at the different exposure levels. It can be seen that the apparent variability [expressed as the  $\log(\text{GSD})$ —the logarithm of the geometric standard deviation of the values in the 8 individuals studied] is larger at the lower exposure level. However the value of the human pharmacokinetic variability indicated here is by no means unusual—it falls at about the 80<sup>th</sup> percentile in my previously collected database of variability in oral human AUC measurements in drugs and other chemicals.

I have a few other suggestions for more modest changes to the parameters used in the model from my earlier work. Briefly, I believe that typical breathing rates for pregnant women are appreciably greater than currently incorporated into the Poet et al. model (Table 2). This would tend to increase the relevant human AUCs further. On the other hand, my previous work has indicated that pregnant women also tend to have more rapid metabolism rates than nonpregnant women for the 7 drugs for which I found data, although there is considerable variation from drug to drug (Table 3). This would tend to reduce central estimates AUCs for parent NMP.

After I generated this initial analysis, EPA was kind enough to point out to me some additional references that could be used to check whether the observed differences in AUC/external dose are found in other sets of observations. Although the specific papers cited by EPA did not provide data detailed enough for a comparable analysis as shown in Table 1, following up on papers cited in those references I found that another paper of Jonsson and Akesson (2003) did provide tabulated results for individual subjects that I could analyze in comparable fashion (Table 4). It can be seen in this table that unlike the Bader and van Thiel observations, there is no tendency of the AUC/(exposure level time) data to decline with increasing exposure levels. However, all three exposure levels yield average AUC/exposure level\*time ratios that are much more similar to those at the lowest exposure level in the Bader and van Thiel study than at the two higher levels—indicating somewhat lower metabolism rates and higher internal doses than would be indicated by the two highest Bader and van Thiel exposure levels.<sup>a</sup>

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<sup>a</sup> Combining data for all three sets of exposures in the Jonsson and Akesson (2003) study yields an average AUC/(exposure level X hours) for their six subjects of 52.6 (std error = 6.7; gmean = 50.3.) When the two higher doses in the Bader and van Thiel study are combined, the average AUC/exposure level for their eight subjects is 24.9 (std error = 1.8; gmean = 24.5). Testing of the logs of these two sets of values indicates that the difference is highly significant ( $P < 0.002$  by t test), although there is some reason for objection to the propriety of formal statistical testing of observations from the two highest exposure Bader and Van Thiel exposure levels only in juxtaposition with all exposure levels from Jonsson and Akesson (2003).

**Table 2**  
**Summary of Data of Garcia-Rio et al. (1996) on Breathing Rates in Pregnant Women vs. the Same Women After Birth**

	N	Week 12	SD	Week 24	SD	Week 36	SD	Postpartum 4 mo	SD
<b>Weight, Kg</b>									
Dyspneic women	11	58	8	63	7	70	7	57	8
Asymptomatic women	12	58	5	64	6	70	7	58	5
<b>VE liters per minute</b>									
Dyspneic women	11	12.15	1.57	12.99	1.76	14.18	1.87	9.6	1.06
Asymptomatic women	12	9.85	1.54	10.49	1.76	11.92	2.02	9.08	1.66
weighted ave at 65 percent dyspneic		11.35		12.12		13.39		9.42	
<b>VE liters per minute per KG BW</b>									
Dyspneic women	11	0.21	0.04	0.21	0.04	0.21	0.04	0.17	0.03
Asymptomatic women	12	0.17	0.03	0.16	0.03	0.17	0.03	0.15	0.03
weighted ave at 65 percent dyspneic		0.196		0.193		0.196		0.163	

**Data Source:** García-Rio F, Pino JM, Gómez L, Alvarez-Sala R, Villasante C, Villamor J. (1996). Regulation of breathing and perception of dyspnea in healthy pregnant women. *Chest*. 110(2):446-453.

**Table 3.** Comparisons of Classical Pharmacokinetic Parameters for Selected Drugs Between Pregnant and Nonpregnant Women

Drug	Elimination Half-Life (minutes)			Volume of Distribution (Liters)			Total Clearance (ml/minute)		
	Pregnant	Nonpregnant	Preg/nonpreg ratio	Pregnant	Nonpregnant	Preg/nonpreg ratio	Pregnant	Nonpregnant	Preg/nonpreg ratio
Ampicillin	52.4	69.6	0.753	32.8	34.5	0.951	450	370	1.216
Cefuroxime	44	58	0.759	17.8	16.3	1.092	282	198	1.424
Imipenem	36	41	0.878	47.1	18.9	2.492	973	338	2.879
Piperacillin	46.5	53.7	0.866	67.6	41.9	1.613	1538	540	2.848
Azlocillin	65.4	72	0.908	15.4	24.7	0.623	126.1	195.7	0.644
Nifedipine	81	360	0.225				266	27	9.852
Labetolol	102	320	0.319				1704	1430	1.192
Sotalol	396	558	0.710	106.4	87.3	1.219	196	109	1.798
		Gmean	0.614			1.212			1.931
		GSD	1.694			1.603			2.272
		Gstd error	1.205			1.212			1.337

**Data Source:** Loebstein R, Lalkin, A, Koren, G. Pharmacokinetic changes during pregnancy and their clinical relevance. Clinical Pharmacokinetics, 1997; 33:328-43.



**Table 4. Analysis of NMP Inhalation Data of Johnson and Akesson (2003)<sup>a</sup> Analogous to Table 1**

Subject	Air		Air		Air	
	Level (mg/m <sup>3</sup> )	AUC/ (hr*mg/m <sup>3</sup> )	Level (mg/m <sup>3</sup> )	AUC/ (hr*mg/m <sup>3</sup> )	Level (mg/m <sup>3</sup> )	AUC/ (hr*mg/m <sup>3</sup> )
1	8	60.4	26	44.8	51	53.7
2	9	49.6	25	80.3	44	64.2
3	13	90.6	24	75.4	55	79.3
4	10	29.7	22	39.4	56	47.1
5	10	43.4	25	33.7	60	50.4
6	12	35.1	23	36.6	54	33.3
Amean, All Subjects	10.3	51.5	24.2	51.7	53.3	54.7
SD, All Subjects		20.1		18.8		14.3
Std Error		8.2		7.7		5.8
Gmean, All Subjects		48.0		48.6		52.8
GSD		1.439		1.410		1.308
log(GSD)		0.158		0.149		0.117

<sup>a</sup> Jonsson, B.A.G. and Akesson, B. (2003). Human experimental exposure to N-methyl-2-pyrrolidone (NMP): Toxicokinetics of NMP, 5-hydroxy-N-methyl-2-pyrrolidone, N-methylsuccinimide and 2-hydroxy-N-methylsuccinimide (2-HMSI) and biological monitoring using 2-HMSI as a biomarker. *Int. Arch. Occup. Environ. Health* 76:267-274.

The reason for this difference in findings is not clear. One possibility is that the higher exposure levels in the Bader and van Thiel study were administered only after a lapse of a week following each lower exposure level. Jonsson and Akesson (2003) unfortunately do not report the length of the lapse of time between the end of their sample collection (48 hours after the end of exposure) until administration of the next exposure. It is possible that the week of time allowed between exposures in the Bader and van Thiel study allowed time for appreciable induction of metabolism, but the possibly shorter time in the Jonsson and Akesson study did not.

EPA has subsequently requested further clarification of my suggestions for the use of the human PBPK model to predict human dose equivalents in the light of these findings I do not suggest that the human PBPK model be discarded in favor of a more traditional dose projection from the animal data. However in the light of the agreement between the results in Table 4 and the low-exposure level results in Table 1 of the overall ratio of human male AUC for plasma NMP per unit of exposure time X exposure level, I think the human model metabolism parameters should be recalibrated and human equivalent doses should be recalculated from the human model after that recalibration. In this recalibration I would exclude the Bader and Van Thiel results for their two higher exposure levels (approximately 40 and 80 mg/m<sup>3</sup>) and include only the plasma NMP levels for the approximately 10 mg/m<sup>3</sup> level in that study, together with the plasma NMP observations for all exposure levels in the Jonsson and Akesson study. The reasons for this are that (1) the plasma AUC data from the two higher exposure levels is clearly inconsistent with the data at the lower level, and with the comparable data at all three exposure levels from the Jonsson and Akesson (2003) study, and (2) the model predictions for the lowest exposure level (for 6-8 hours of exposure) are likely to be more directly relevant to actual conditions of exposure of pregnant women whose developmental exposure risks are being assessed. After the recalibration of metabolism rates for the males, further adjustment for pregnancy-related changes in metabolism rates can then be applied based on the data provided in Table 3.

**Question 8-2:** Please comment on the appropriateness of using the selected dose metric for chronic inhalation and dermal exposures based on the maternal blood concentration of the parent compound expressed as the area under the curve (AUC). Please comment on whether the maternal dose metric is a reasonable surrogate for a fetal dose metric in the absence of fetal metabolism data.

**I think AUC averaged over the period of pregnancy, but particularly the latter half of pregnancy is the best choice of dose metric for projecting between rats and humans. EPA's analysis indicating lower AUCs associated with fetal growth inhibition effects in the study that exposed through the end of pregnancy (Saillenfait) rather than the earlier study that stopped exposure at day 15 or so, clearly points to this conclusion.**

**Question 8-3:** Please comment on whether the selected dose metric for acute inhalation and dermal exposures should be reported as the maternal blood AUC of the parent compound and/or the maximum concentration (C<sub>max</sub>) in maternal blood.

**I think the maternal blood AUC of the parent compound is the best choice as supported in the EPA analysis.**

**Question 8-4:** Please comment on whether the BMD analysis should be conducted with the PBPK-derived internal doses or the external air concentrations (standard approach) reported in Saillenfait et al. 2003. Please specify whether the BMD calculations (Appendix F of draft risk assessment) were appropriately conducted and documented.

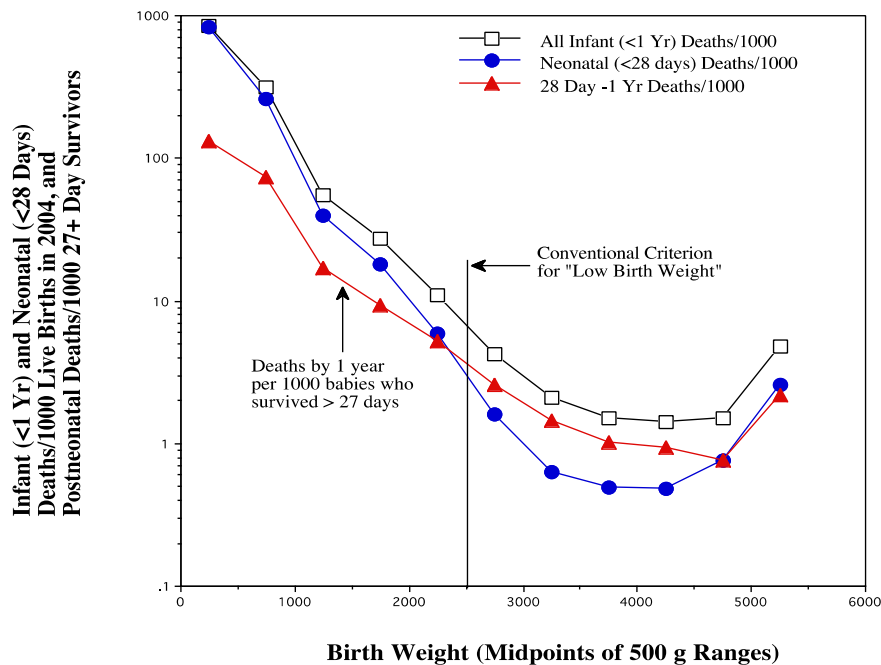
**I believe these calculations should be redone based on a revised PBPK model that takes into account the apparently slower metabolism of NMP indicated at the lower exposure level in the Bader and van Thiel data, as indicated above, combined with the comparable metabolism rate indicated for all three exposure levels in Jonsson and Akesson (2003) study.**

## Questions on the Risk Assessment

**Issue 9.** The margin of exposure ( MOE) approach used the PODs identified in the hazard/dose-response assessment to evaluate risks for the acute and chronic inhalation and dermal exposures to NMP-based paint strippers. The new preferred approach consists of estimating MOEs based on the PBPK-derived internal doses estimated for the selected POD and the human exposure level calculated in the occupational or the consumer exposure analysis (refer to PBPK modeling appendix and EPA’s overview presentation). The MOE is the ratio of the *POD* internal dose to the *Exposure internal dose*. MOE calculations with internal doses facilitate combining dermal and inhalation exposures and are thus preferred over the estimation of human equivalent concentrations/doses (HEC/HED). MOEs were compared to benchmark MOEs to determine whether potential risks were present for the different exposure scenarios. Benchmark MOEs were assigned to each exposure scenario depending on the uncertainties of the PODs chosen for the analysis. The risk characterization also provides a discussion of the uncertainties surrounding the risk calculations.

**Question 9-1:** Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the acute inhalation risks to consumers of NMP-based products and to bystanders/non-users (e.g., children, women of childbearing age), including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HECs. Please comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the acute inhalation risks.

**The MOE approach can be a defensible guide as long as the POD chosen is a reasonable approximation of a level that is expected to represent a minimal effect. That is not the case with the current 5 percent change in fetal weight. Birth weight is very strongly associated with infant mortality in people, as indicated in the figure below, based on US data from 2004:**



**Source:** Hattis D. and Chu, W. “Maternal cigarette smoking and human birth weight : patterns of change, risks of associated outcomes, and implications for environmental chemicals”

**If a 5 percent change in fetal weight were to directly translate into a similar change in human birth weights it would be expected to be associated with a change in infant mortality similar to that produced by direct cigarette smoking, causes a change of the order of 6 percent in average birth weights. Using the relationship between birth weight and infant mortality, I projected some years ago that even a 1 percent change in birth weights across the whole birth weight distribution in people would be expected to be associated with about a 0.27/1000 increase in the incidence of infant deaths per live birth (see Table 5 below). I think this means that a POD for fetal growth inhibition should be set to much less than the 5 percent level used for the current calculations.**

**Table 5**

**Expected Effect on Infant Mortality of an Agent that Causes a 1 percent Decrease in Birth Weight and Whatever Causal Variables are Associated with Birth Weight to Produce Infant Mortality**

Birth Weight Range (500g Intervals)	Excess Neonatal Death Rate/1000 Live Births from 1% Birth Weight Shift	Excess Postneonatal Death Rate/1000 Live Births from 1% Birth Weight Shift	Excess Total Infant Death Rate/1000 Live Births from 1% Birth Weight Shift
Less than 500 grams	0.0346	0.0010	0.0355
500-999 grams	0.0797	0.0174	0.0972
1000-1499 grams	0.0152	0.0062	0.0214
1500-1999 grams	0.0235	0.0119	0.0353
2000-2499 grams	0.0290	0.0257	0.0546
2500-2999 grams	0.0219	0.0347	0.0565
3000-3500 grams	0.0021	0.0047	0.0067
3500-3999 grams	-0.0071	-0.0148	-0.0219
4000-4499 grams	-0.0037	-0.0072	-0.0109
4500-4999 grams	-0.0011	-0.0011	-0.0023
5000+ grams	-0.0004	-0.0004	-0.0008
Total <2500 g	0.1819	0.0621	0.2440
Total 2500+g	0.0116	0.0158	0.0274
Total, all birth weights	0.193	0.078	0.271
% of Deaths <2500 g	94.0	79.7	89.9

**Source:** Hattis D. and Chu, W. “Maternal cigarette smoking and human birth weight: patterns of change, risks of associated outcomes, and implications for environmental chemicals” Poster presented at the 2011 Society for Risk Analysis Annual Meeting

**Question 9-2:** Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the chronic inhalation risks to workers using NMP-based products, including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HECs. Please also comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the chronic inhalation risks.

**My response to this is similar to that for 9-1. I would lower the POD considerably to help guard against both infant mortality and other effects associated with even modestly lowered birth weights from chronic occupational exposure of pregnant workers. Otherwise, with the changes I have suggested in the PBPK modeling, I think it is fine to project from rats to people using internal AUCs.**

**Question 9-3:** Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the acute dermal risks to consumers of NMP-based products, including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HEDs. Please also comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the acute dermal risks.

### Similar comment.

**Question 9-4:** Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the chronic dermal risks to workers of NMP-based products, including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HEDs. Please also comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the chronic dermal risks.

### Similar comment.

**Question 9-5:** Please comment on whether the risk assessment document has adequately described the uncertainties and data limitations in the methodology used to assess risks to allow the EPA to reduce risks to human health from NMP. Please comment on whether this information is presented in a transparent manner.

**Some additional comment is I think needed because of the necessary projection of metabolism rates between human males and females, and between non-pregnant and pregnant women. The comparison of AUCs resulting from comparable dermal exposures of men vs. nonpregnant women in Table 4 of Akesson et al. (2004)<sup>a</sup> (50 vs. 53  $\mu\text{mol}\cdot\text{hr}/\text{l}$  median plasma AUCs for comparable dermal exposures and urinary metabolite excretion) seem to indicate roughly similar metabolism rates between the sexes.**

### Reference:

Keener SA, Wrbitzky R, Bader M (2007) Human volunteer study on the influence of exposure duration and dilution of dermally applied N-methyl-2-pyrrolidone (NMP) on the urinary elimination of NMP metabolites. *Int Arch Occup Environ Health* 80:327-334.

### EPA's Clarifying Questions for the Peer Review Panel Reviewing the Draft Risk Assessments for N-Methylpyrrolidone (NMP)

1. Regarding Dr. Dale Hattis' comments on page 30, Question 8-4:  
The comment states support for use of the PBPK model-predicted internal doses to predict internal doses which are then used for BMD modeling.
  - a) First we note that the BMD modeling is being conducted with the rat toxicity data and, to that point, only involves use of the rat PBPK model. The Bader and van Thiel data which may indicate slower metabolism at lower exposures are human PK data, not necessarily relevant to the rat. Therefore it appears the review is *not* suggesting that we revise the rat PBPK model before using it to estimate internal doses, and the reviewer is supportive of using the rat-PBPK-model-predicted internal doses for PBPK modeling. Please clarify your evaluation of the usability of the *rat* PBPK model without changes to address this exposure-response issue.

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<sup>a</sup> Akesson, B., Carnerup, M.A., and Jonsson, B.A.G. (2004). Evaluation of exposure biomarkers from percutaneous absorption of N-methyl-2-pyrrolidone. *Scand. J. Work. Environ. Health* 30(4):306-312.

**I have no difficulty with the use of the rat PBPK model to assess internal rat doses. I do suggest use of a different benchmark response level much lower than the 5 percent fetal weight reduction used in the prior analysis.**

- b) Second, we understand that the reviewer is suggesting that the human PBPK model be revised before it is used to estimate human internal doses for comparison to the rat internal BMDLs. However, as previously indicated, we are uncertain that the total human data set is consistent with the atypical exposure-dose relationship seen in the Bader and van Thiel data. Even if metabolic induction is occurring, that is a dynamic (time-dependent) process, and additional human PK data may be needed to properly describe it, without making a number of highly uncertain assumptions. So we wish to clarify that the reviewer is suggesting that EPA *not* use the PBPK modeling, but a default approach, if examination of the larger data set indicates this is a real phenomenon and we are unable to revise the human PBPK model accordingly.

**I do not suggest that the human PBPK model be discarded in favor of a more traditional dose projection from the animal data. However in the light of the agreement between the results in Table 4 and the low-exposure level results in Table 1 of the overall ratio of human male AUC for plasma NMP per unit of exposure time X exposure level, I think the human model metabolism parameters should be recalibrated and human equivalent doses should be recalculated from the human model after that recalibration. In this recalibration I would exclude the Bader and Van Thiel results for their two higher exposure levels (approximately 40 and 80 mg/m<sup>3</sup>) and include only the plasma NMP levels for the approximately 10 mg/m<sup>3</sup> level in that study, together with the plasma NMP observations for all exposure levels in the Jonsson and Akesson study. The reasons for this are that (1) the plasma AUC data from the two higher exposure levels is clearly inconsistent with the data at the lower level, and with the comparable data at all three exposure levels from the Jonsson and Akesson (2003) study, and (2) the model predictions for the lowest exposure level (for 6-8 hours of exposure) are likely to be more directly relevant to actual conditions of exposure of pregnant women whose developmental exposure risks are being assessed. After the recalibration of metabolism rates for the males, further adjustment for pregnancy-related changes in metabolism rates can then be applied based on the data provided in Table 3 of my comments.**



## Ronald D. Hood

OPPT focused its risk assessment on the use of NMP in paint stripping. There are human health concerns for developmental effects related to NMP use-application. Both inhalation and dermal exposures were evaluated and risk estimates were calculated for consumers and workers using NMP-based paint strippers. Risks also were estimated for individuals physically near the residential user, but not using the NMP-based product (also referred to as bystanders or non-users).

### General Question on the Risk Assessment Document

**Issue 1.** This risk assessment is divided into three chapters with seven appendices. Chapter 1 describes the scope for the NMP human health risk assessment. Chapter 2 provides information on chemistry, environmental fate and transport, production, and uses. Chapter 3 characterizes exposure, hazard, and risk findings as well as the uncertainties of the assessment. Supporting information is provided in the appendices. The risk assessment is intended to provide a clear and transparent summary of the Agency's analysis.

**Question 1-1:** Please comment on whether the risk assessment provides a clear and logical summary of EPA's analysis. Please provide specific suggestions for improving the clarity and transparency of the risk assessment document.

Reviewer's response: The following statement is from the Executive Summary. "NMP was identified for assessment based on high concern for hazard due to its reproductive toxicity, although the inclusion of more recent studies in this assessment indicates that NMP is of low concern for this endpoint." It would be helpful if the term "reproductive toxicity" were clarified as to whether it meant effects on fertility, on development, or both. Other parts of the document refer to "developmental toxicity," but the term "reproductive toxicity" does not seem to have been used again.

Also, the final paragraph on page 45, reproduced here, seems incomplete:

"It is interesting to note that there is evidence to support that absorption and effect are very similar by oral and dermal routes. Oral LD50 values were 4,150, 3,914 and 3,605 mg/kg in rats (Ansell and Fowler, 1988; Bartsch et al., 1976; BASF AG, 1963; as cited in OECD, 2007, respectively) and 7,725 and 4,050 mg/kg in mice (Bartsch et al., 1976; Weisbrod and Seyring, 1980; Weisbrod, 1981; as cited in OECD, 2007) to dermal dose levels."

And on page 49, in this heading, "*Rational for Study and Endpoint Selection for Acute PODs.*" "*Rational*" should be "*Rationale.*"

In Table F-1, the column heading refers to "fetuses," but the data are actually numbers of litters examined.

**Question 1-2:** Please comment on whether appropriate background information is provided and accurately characterized. Please provide any other relevant literature, reports, or data that would be useful to support the risk assessment.

The following two papers present some data of interest:

Sitarek K, Stetkiewicz J. 2008. Assessment of reproductive toxicity and gonadotoxic potential of N-methyl-2-pyrrolidone in male rats. *Int. J. Occup. Med. Environ. Health* 21(1):73-80.

Sitarek, K., Stetkiewicz, J., and Wąsowicz, W. 2012. Evaluation of reproductive disorders in female rats exposed to N-methyl-2-pyrrolidone. *Birth Defects Res., Part B. Devel. Reprod. Toxicol.* 95(3):195-201.

## **Questions on the Exposure Assessment**

### **--Inhalation Exposures**

**Issue 2. EPA found limited published data for NMP's air concentrations in workplace settings during use of NMP-based paint strippers. These data were used for estimating occupational inhalation exposures to NMP in adult workers (e.g., male and female workers of childbearing age).**

**Question 2-1:** Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of the workplace inhalation exposure, including specific citations (if available) of data sources characterizing occupational inhalation exposures.

Reviewer's response: This question is outside of this reviewer's area of expertise.

**Issue 3. EPA conducted a literature review and found insufficient data to characterize inhalation exposures for residential users (e.g., adult users including women of childbearing age) and bystanders/non-users (i.e., children, women of childbearing age). Therefore, EPA used a modeling approach to estimate inhalation exposures. EPA found limited data on consumer uses and profiles and conducted a sensitivity analysis of model parameters to identify critical parameters essential to the inhalation modeling approach. EPA varied the most sensitive input parameters to generate central tendency and upper-end NMP air concentrations. 2**

**Question 3-1:** Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of consumer inhalation exposure, including specific citations of data sources characterizing consumer emission profiles of NMP-based paint strippers. As part of the review, please also evaluate the sensitivity analysis conducted for the assessment and comment on the strengths and weaknesses of the evaluation of different exposure scenarios and the choice of assumptions/input parameters for generating central tendency and upper-end NMP air concentrations.

Reviewer's response: This question is outside of this reviewer's area of expertise.

### **--Dermal Exposures**

**Issue 4. No data were found for occupational or consumer dermal exposures to NMP-based paint strippers. Thus, modeling approaches were used to estimate potential dermal exposures of adult users in contact with liquid NMP-based paint strippers at workplace**

**and residential settings. The occupational and consumer dermal exposure estimates use similar “thin-film” modeling approaches. A primary difference between the approaches is the film thickness assumption. The estimates for occupational exposures are based on a range of film thickness values from laboratory tests of surrogate film materials. The film thickness value for consumer exposures was based on the professional judgment of a chemist employed in a paint stripping company.**

**Question 4-1:** Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of the workplace dermal exposure, including specific citations (if available) of data sources characterizing occupational dermal exposures. Please comment on the strengths and weaknesses of the evaluation and the choice of assumptions/input parameters for generating estimates of the NMP’s dermal exposure.

Reviewer’s response: This question is outside of this reviewer’s area of expertise.

**Question 4-2:** Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of the consumer dermal exposure, including specific citations (if available) of data sources characterizing dermal exposures in a residential setting. As part of the review, please comment on the strengths and weaknesses of the evaluation and the choice of assumptions/input parameters for generating estimates of the NMP’s dermal exposure.

Reviewer’s response: This question is outside of this reviewer’s area of expertise.

**Question 4-3:** Please comment on the assumptions used by the Agency regarding film thickness for the assessment, including any additional data on film thickness with which to assess dermal exposure to NMP for both consumers and workers.

Reviewer’s response: This question is outside of this reviewer’s area of expertise.

## **Questions on the Hazard Assessment**

**Issue 5. EPA chose a point of departure (POD) from developmental inhalation studies in rats reported by Saillenfait et al. (2001, 2003)<sup>1</sup> to assess the acute inhalation scenario. It was assumed that a single exposure to NMP could be sufficient to produce adverse developmental effects (US EPA, 1991; van Raaij et al., 2003)<sup>2</sup>. From the Saillenfait studies, EPA chose a POD based on fetal body weight decrements to represent the effects of single acute inhalation exposure.**

**Question 5-1:** Please comment on EPA’s use of the identified developmental studies and POD to assess acute inhalation exposures to NMP use in paint strippers. As part of the review, provide your input on the appropriateness of using an acute POD based on fetal body weight decrements that were observed in the presence of maternal body weight decrements following exposure to NMP during gestational days 6 to 13. Please comment on whether the maternal no-observed-adverse-effect level (NOAEL) of 122 mg/m<sup>3</sup> (Saillenfait et al. 2001, 2003) should be analyzed in the MOE calculations along with the fetal body weigh decrements. Please specify any other endpoints that should be considered for the hazard evaluation of acute inhalation exposures.

Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.

*Reviewer's response:* As can be inferred from the charge question, use of multiple-dose developmental toxicity studies as the basis for determining an acute POD is not ideal. Presumably it was done in the current case because of the lack of single dose studies using developmental toxicity endpoints, and also because the identified NOAEL was lower than those identified from studies employing other toxicity endpoints. Further, the Saillenfait et al. (2003) study employed inhalation exposures, making it potentially somewhat more suitable for extrapolation to human inhalation exposures than studies that relied upon oral or dermal exposures. However, as pointed out by van Raaij et al. (2003), "The relevance of fetal body weight (and retarded ossification) for acute limit setting should be evaluated within the total context of developmental effects and maternal toxicity." Moreover, as van Raaij et al. also stated, "Using a NOAEL from a normal 'guideline-based' repeated dose developmental toxicity study always provides a worst case estimation of the NOAEL in a single dose exposure." EPA's stated goal in the current NMP Draft Risk Assessment is to be highly conservative in the choice of a POD from the studies available. According to the NMP Draft Risk Assessment, "EPA chose to use a conservative approach to protect susceptible populations (i.e., women of childbearing age and pregnant women)." In that regulatory context, the current NMP Draft Risk Assessment has likely met the stated goal. On the other hand, if a perhaps more realistic MOE is the goal, then use of data from a guideline compliant developmental toxicity study, which uses multiple treatment days, may not be ideal. However, the EPA cannot in this context require performance of one or more potentially more relevant studies, so obtaining more data is not currently an option.

Also, it is worthwhile to address the issue of whether the observed fetal body weight decrements were caused by direct exposure of the conceptus to NMP (and/or its metabolites) or if they were maternally-mediated (i.e., caused indirectly, as a result of maternal toxicity). And of course decreased fetal weight could be caused by a combination of direct and indirect effects. If the answer to this question were known, it would be more obvious to what degree the maternal MOE should be of concern when extrapolating to the human. However, it must be understood that definitively answering the question of direct vs. indirect effects is often impossible from the limited amount of data typically available. Reduced fetal weights at term can be due to reduced maternal food intake resulting from general toxicity to the dam, rather than being due to a direct developmental insult to the conceptus (Fleeman et al., 2005; Beyer et al., 2011). (And in studies employing exposure via test agent incorporation in the diet, it can be a consequence of maternal taste aversion.) However, determining which alternative was likely to have been the case in a given developmental toxicity study would require additional testing, such as use of pair-feeding. Such additional testing is only rarely done, and in the case of NMP, no such studies are currently available, nor is it anticipated that they will ever be available.

More specifically, according to the data presented by Saillenfait et al. (2003), maternal body weight gain was significantly decreased at both the middle and high dose (243 and 487 mg/m<sup>3</sup>, 6 h/day from gestation day 6 through 20), with a maternal NOAEL of 122 mg/m<sup>3</sup>. However, it is unclear if the effect of NMP exposure on maternal body weight was related to decreased feed consumption, as that parameter appeared to have been decreased at the middle dose, but the difference from the control value was statistically significant at the high dose only. The measured decrease in feed consumption, in the vicinity of 2 grams per day, may have been adequate to cause the observed lower fetal weights, especially at the high NMP dose (Fleeman et al., 2005). Fetal body weights were statistically significantly decreased at the high dose only, resulting in a NOAEL of 243 mg/m<sup>3</sup>. However, fetal weights at the 243 mg/m<sup>3</sup> dose level were

lower than control weights, and thus were suggestive of a treatment effect. These findings indicate that maternal toxicity, as manifested by the effect on maternal body weight, had occurred at the same or possibly at a lower NMP exposure than the exposure level affecting the conceptus.

It should be also be noted that the apparent maternal toxicity observed at exposures of 243 mg/m<sup>3</sup> and above by Saillenfait et al. (2003) was not seen in a similar rat inhalation study at a maternal exposure level of 669 mg/m<sup>3</sup> for 6 h per day from gestation days 4-20 (Hass et al., 1995). Moreover, in a In a two-generation reproduction study, including a fetal evaluation of controls and a high dose group only, female rats were exposed by inhalation to NMP at concentrations of 0, 40.5, 207, or 470 mg/m<sup>3</sup> for 6 h/day, 7 days/week, from 34 days of age and continuing through mating until day 20 of gestation. In that study, no effect on maternal body weight was noted, but the rats allowed to deliver were weighed on gestation days 1 and 21 and postpartum only, while dams in a group used for developmental toxicity assessment were apparently weighed at sacrifice (Solomon et al., 1995). Decreased pup birth weight and decreased fetal weight were noted at the 470 mg/m<sup>3</sup> dose only, but no lower dosage groups were included for the fetal assessments. There were no observed effects on offspring morphology or survival.

To further complicate the issue, Saillenfait and colleagues published an embryo-fetal toxicity study in rats with oral NMP exposures of 0, 125, 250, 500, and 750 mg/kg/d (Saillenfait et al., 2002), in which the developmental toxicity LOAEL (based on decreased fetal weights and increased malformations) was 250 mg/kg/d. Prenatal mortality and malformations were increased at the two higher dosages, and one malformation (anal atresia plus tail absent or vestigial) seen in 7 fetuses from 5 different litters) was also observed in a single fetus from a dam exposed at the 250 mg/kg/d dosage level. It is not entirely clear, however, that 250 mg/kg/d was truly the maternal NOAEL, as stated by the study's authors, because the maternal body weight gain may possibly have been decreased at that dosage, though not statistically significantly, as that parameter was quite variable.

When considering whether a modest decrease in fetal weight, as seen in Saillenfait et al. (2003), is an effect of prenatal exposure to NMP, additional factors should be considered. For example, there were no other indications of adverse effects on the conceptus, thus diminishing the certainty that the observed differences in fetal weight were actually due to developmental toxicity (Stump et al., 2012). Even more critical is whether the fetal weights of the presumably affected group were within or outside of the range of recent historical controls, preferably from the laboratory that conducted the published research. Although historical control data are generally available in the study reports of guideline compliant studies conducted for regulatory purposes, they are often not included in published reports, and that was the case with Saillenfait et al. (2003). Nevertheless, as suggest by outside commenters, a contemporary historical control database could be constructed by compiling the published control data derived from the same laboratory during the years around the year during which the relied upon study was conducted.

Decreased fetal body weight that appears to have been secondary to decreased maternal food consumption, with no other adverse maternal findings, generally would not be considered evidence of *compound-specific* developmental toxicity. However, a conclusion that such an apparent effect is maternally-mediated would be more convincing if based on experimental evidence that reduced fetal body weight was greater in those litters from mothers with decreased

food consumption (Beyer et al., 2011). In other words, it would preferably be based on examination of the relationship using data from individual animals, rather than the group mean. However, as is the case with the Saillenfait et al. (2003) study, the relevant data are not often readily available from studies as published.

One additional factor in assessing the developmental toxicity potential that should be addressed in the NMP Draft Risk Assessment is the report by Saillenfait et al. (2007) that evaluated the comparative developmental toxicity of the three major metabolites of NMP after gavage dosing of pregnant rats. According to that report, the metabolites are less toxic than the parent compound. NMP is apparently largely metabolized, especially after inhalation exposure, according to the OECD (2007) (as reported in the current Draft Risk Assessment). Further, the relative biotransformation of NMP in rats and humans is of interest. Such metabolism can be a significant factor to consider in evaluating the risks for developmental toxicity associated with human exposure. Biotransformation of NMP in rats was addressed by Carnerup and colleagues (2005).

In summary, the use of Saillenfait et al. (2003) as the basis for setting NMP exposure limits, especially in the case of acute exposures, is relatively conservative. Not only is there uncertainty regarding the fetal weight parameter relied upon, but there is also a considerable likelihood that an acute exposure at the dose level used would not have caused a biologically significant effect on fetal weight. Although malformations can be induced with single exposures in many cases, the concept of critical periods of development is likely less reliable when considering effects on *growth* of the conceptus. That belief was supported by van Raaij et al. (2003), who stated that for the majority of the substances they studied, “. . . the NOAELs and LOAELs of the single dose studies are about 200-400 percent of the repeated dose values, indicating 2-4 fold higher dosages are needed in a single day study to induce a decrease in fetal body weight.” Further, the gestation length of a rat is only 22 days on average, so each day of exposure in that species encompasses significantly more critical developmental events than is the case for a developing human. This makes the multiple day exposure used by Saillenfait et al. (2003) even more like a chronic exposure, rather than modeling an acute exposure for a pregnant woman.

In response to the question whether the maternal no-observed-adverse-effect level (NOAEL) of 122 mg/m<sup>3</sup> (Saillenfait et al. 2001, 2003) should be analyzed in the MOE calculations along with the fetal body weight decrements, it is uncertain how much added value would accrue to the risk assessment from such an analysis, considering the uncertain relationship of the apparent maternal NOAEL to the observed fetal effects.

With regard to the use of the identified developmental toxicity studies cited, it is less than ideal that the NMP Draft Risk Assessment cited a secondary source of information found in a poster presentation (Saillenfait et al., 2001), rather than the full publication (Saillenfait et al., 2003) that followed. Moreover, the poster presentation had apparently not been reviewed directly. Instead, the NMP Draft Risk Assessment depended on an evaluation from a prior review, i.e., OECD (2007), from another regulatory body.

**Issue 6. EPA also chose to use the developmental inhalation studies in rats reported by Saillenfait et al. (2001, 2003) to evaluate the chronic occupational inhalation exposures. It was assumed that the repeated nature of exposure to NMP during pregnancy could**

**produce adverse developmental effects. From these studies, EPA chose a POD based on decrements in fetal body weight to represent the effects of chronic inhalation exposure.**

**Question 6-1:** Please comment on EPA's use of the identified developmental studies and POD to assess chronic inhalation exposures. As part of the review, please comment on the appropriateness of using a developmental toxicity endpoint and the identified effects to assess chronic inhalation exposures to NMP-based paint strippers. Please specify any other toxicological endpoints that should be considered for the hazard evaluation of acute inhalation exposures. Also, please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.

*Reviewer's response:* As explained above, use of a typical developmental toxicity study, such as Saillenfait et al. (2003), appears more justifiable for setting a POD for chronic exposures than for acute exposures, as such studies most often employ multiple exposures. Moreover, as mentioned previously, the experimental exposure route for the identified key study is the same as the route of the human exposures under consideration. Nevertheless, most of the other concerns and considerations described above in response to Question 5-1 are relevant here. However, in this case, a POD as determined in the current NMP Draft Risk Assessment is likely to have been somewhat more realistic in terms of its prediction of potential risk of developmental toxicity, as exposure covered most of gestation, and included the periods of major organogenesis and skeletal maturation.

Fetal body weight as a toxicity endpoint, especially for developmental toxicity evaluation, is generally less variable and more sensitive than other developmental toxicity parameters (Stump et al., 2012). Fetal weight is thus the most common endpoint used for setting NOAELs and LOAELs for developmental toxicity (Chernoff et al., 2008), and it is likely to be the most reliable/reproducible.

**Issue 7. EPA chose a developmental dermal study in rats to characterize acute and chronic hazard for the dermal exposure scenario. The POD was based on fetal body weight and fetal death to represent the effects of acute and chronic dermal exposure.**

**Question 7-1:** Please comment on EPA's use of the identified developmental study and POD to assess acute and chronic dermal exposures. As part of the review, provide your input on the appropriateness of using a developmental toxicity endpoint and the identified effects to assess acute and chronic dermal exposures to NMP-based strippers. Please specify any other endpoints that should be considered for the hazard of acute or chronic dermal exposures. Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.

*Reviewer's response:* Although not named above, and not clearly identified as such in the NMP Draft Risk Assessment, the study referred to was obviously Becci et al. (1982), which described the outcomes of dermal administration of NMP to pregnant rats at exposures of 75, 237, or 750 mg/kg/d. Becci et al. found the NOAEL to be 237 mg/kg/d for both maternal and fetal effects, a result that is in agreement with the likelihood of similar susceptibilities of mother and conceptus to adverse effects of NMP exposure. Such an outcome is unsurprising, as it appears to be the case in a significant percentage of developmental toxicity studies done with rats (Chernoff et al.,

2008), and it is not unlike the possible maternal and fetal toxicity relationship associated with NMP exposure by inhalation, as seen by Saillenfait et al. (2003).

As to whether the dermal developmental toxicity study of Becci et al. (1982) is appropriate to provide the basis for both acute and chronic dermal exposure PODs, again it is not ideal. It provides a basis for highly protective MOE estimates, which is EPA's stated goal. However, it suffers from the known limitations in extrapolating the results of rat dermal exposures to human dermal exposures, in that the permeability characteristics of rat and human skins are dissimilar. Also, Becci et al. (1982) imperfectly models both acute and chronic exposure scenarios. That study included multiple exposures, but those exposures did not include the later days of rat gestation (after day 15). The exposure timing employed by Becci et al. (1982) did cover the developmental period during which malformations are likely to be induced by teratogenic exposures. However, these exposures did not cover the gestation days during which bone ossification can best be evaluated. They also did not cover the gestation days during which effects on fetal body weight are most likely to be induced and/or detected. That is because if there are adverse effects on the conceptus caused by exposures during mid-gestation, and those exposures do not continue into late gestation, the fetus may have time to partially or fully compensate in growth before the day of termination (Chernoff et al., 2008). Also, because the fetus is gaining most of its weight during late gestation, maternal exposure during that time is likely to have a greater effect on prenatal growth than would earlier exposure (Chernoff et al., 2008).

**Issue 8. EPA evaluated whether a physiologically-based pharmacokinetic (PBPK) model could be used in the NMP workplan risk assessment. Poet et al. (2010) constructed a PBPK model to describe the toxicokinetics of NMP in pregnant rats and humans after oral, dermal and inhalation exposures to NMP. The authors used PBPK and benchmark dose (BMD) methodologies to estimate human equivalent concentrations/doses (HEC/HED) based on a POD for fetal body weight. EPA evaluated the model during the development of the draft NMP risk assessment, but did not use the original model due to uncertainties in the model parameterization. The authors have recently revised the model and submitted it to EPA for further consideration. EPA has reviewed the revised PBPK model and determined that it is appropriate for risk assessment purposes. A copy of the model evaluation report and the model files (including the code) has been posted in the NMP docket. EPA intends to use the revised model to evaluate the risks of acute and chronic inhalation and dermal exposures to NMP-based paint strippers.**

**Question 8-1:** Please review the model and comment on the Poet et al. (2010) analysis as well as EPA's evaluation of the revised model. Please comment on whether the model is clearly and transparently described and technically and scientifically adequate for supporting OPPT's workplan risk assessment for NMP-based paint strippers. Specifically, please address the structure of the PBPK model, parameter calibration and model predictions of the available *in vivo* data.

Reviewer's response: This question is outside of this reviewer's area of expertise.

**Question 8-2:** Please comment on the appropriateness of using the selected dose metric for chronic inhalation and dermal exposures based on the maternal blood concentration of the parent compound expressed as the area under the curve (AUC). Please comment on whether the



maternal dose metric is a reasonable surrogate for a fetal dose metric in the absence of fetal metabolism data.

Reviewer's response: In the absence of data from human embryos or fetuses there is little alternative to this use of maternal blood concentration.

**Question 8-3:** Please comment on whether the selected dose metric for acute inhalation and dermal exposures should be reported as the maternal blood AUC of the parent compound and/or the maximum concentration (C<sub>max</sub>) in maternal blood.

Reviewer's response: In the absence of actual developmental toxicity study data comparing the effects of higher peak blood concentrations versus lower but more sustained exposures, the choice of dose metric remains relatively speculative.

**Question 8-4:** Please comment on whether the BMD analysis should be conducted with the PBPK-derived internal doses or the external air concentrations (standard approach) reported in Saillenfait et al. 2003. Please specify whether the BMD calculations (Appendix F of draft risk assessment) were appropriately conducted and documented.

Reviewer's response: The use of a PBPK modeling approach is likely to be more informative, especially if it takes into account the likely changes in NMP concentrations in the maternal and fetal compartments over the course of gestation.

## Questions on the Risk Assessment

**Issue 9. The margin of exposure (MOE) approach used the PODs identified in the hazard/dose-response assessment to evaluate risks for the acute and chronic inhalation and dermal exposures to NMP-based paint strippers. The new preferred approach consists of estimating MOEs based on the PBPK-derived internal doses estimated for the selected POD and the human exposure level calculated in the occupational or the consumer exposure analysis (refer to PBPK modeling appendix and EPA's overview presentation). The MOE is the ratio of the *POD<sub>internal dose</sub>* to the *Exposure internal dose*. MOE calculations with internal doses facilitate combining dermal and inhalation exposures and are thus preferred over the estimation of human equivalent concentrations/doses (HEC/HED). MOEs were compared to benchmark MOEs to determine whether potential risks were present for the different exposure scenarios. Benchmark MOEs were assigned to each exposure scenario depending on the uncertainties of the PODs chosen for the analysis. The risk characterization also provides a discussion of the uncertainties surrounding the risk calculations.**

**Question 9-1:** Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the acute inhalation risks to consumers of NMP-based products and to bystanders/non-users (e.g., children, women of childbearing age), including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HECs. Please comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the acute inhalation risks.

Reviewer's response: This question is outside of this reviewer's area of expertise.

**Question 9-2:** Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the chronic inhalation risks to workers using NMP-based products, including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HECs. Please also comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the chronic inhalation risks.

Reviewer's response: This question is outside of this reviewer's area of expertise.

**Question 9-3:** Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the acute dermal risks to consumers of NMP-based products, including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HEDs. Please also comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the acute dermal risks.

Reviewer's response: This question is outside of this reviewer's area of expertise.

**Question 9-4:** Please comment on the assumptions, strengths and weaknesses of the MOE approaches used to estimate the chronic dermal risks to workers of NMP-based products, including the standard MOE approach presented in the document as well as MOEs calculated with PBPK-derived internal doses instead of HEDs. Please also comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the chronic dermal risks.

Reviewer's response: This question is outside of this reviewer's area of expertise.

**Question 9-5:** Please comment on whether the risk assessment document has adequately described the uncertainties and data limitations in the methodology used to assess risks to allow the EPA to reduce risks to human health from NMP. Please comment on whether this information is presented in a transparent manner.

Reviewer's response: This has been addressed in this reviewer's responses to previous questions.

#### **References Cited in Responses to Questions Regarding Issues 5, 6 and 7**

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[http://www.rivm.nl/dsresource?objectid=rivmp:16116&type=org&disposition=inline&ns\\_nc=1](http://www.rivm.nl/dsresource?objectid=rivmp:16116&type=org&disposition=inline&ns_nc=1)

## **John Kissel**

### **General Question on the Risk Assessment Document**

*Question I-1: Please comment on whether the risk assessment provides a clear and logical summary of EPA’s analysis. Please provide specific suggestions for improving the clarity and transparency of the risk assessment document.*

Many of the documents cited in support of the risk assessment are not in the public domain. Disclosure of the contents of industry submissions undoubtedly creates difficulties for EPA. However, transparency cannot be achieved if information utilized in preparation of risk assessments is held to be confidential, or even if not confidential, is not accessible.

### **Questions on the Exposure Assessment**

*Question 4-1: Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of the workplace dermal exposure, including specific citations (if available) of data sources characterizing occupational dermal exposures. Please comment on the strengths and weaknesses of the evaluation and the choice of assumptions/input parameters for generating estimates of the NMP's dermal exposure.*

The worker dermal exposure scenarios include assumptions that could be considered both conservative and non-conservative. Conservative assumptions include no use of gloves (although under limited conditions, poorly chosen or poorly employed gloves can increase rather than decrease exposure), use of stripper containing 100 percent NMP, and 100 percent absorption of deposited liquid. (Note that 100% absorption was assumed in the tabulated scenarios for which MOEs were calculated. Simulations run using the PBPK model [which are not presented in the RA document, but were provided with ancillary materials] utilize gradient driven uptake rather than fixed percentage absorption.)

Variable skin loads of 0.7-2.1 mg/cm<sup>2</sup> were considered. While no primary data are available, these adherence factors are plausible as spot measurements. Non conservative assumptions include exposure to hands only, and only one exposure event per day (although that one event engaged 100 percent of the hand surface area). Generally occupational dermal exposures are expected to occur repeatedly over the course of the work day. Hughson and Aitken (*Ann Occup Hyg*, 2004) investigated dermal exposures to hands and rest-of-body from three job tasks (spray painting, wiping surfaces, and mixing/dilution of formulation) and found geometric mean exposure rates of 0.01-139 mg/cm<sup>2</sup>/hr. Assuming an 8-hr shift, a single 0.7-2.1 mg/cm<sup>2</sup> exposure translates to 0.09-0.25 mg/cm<sup>2</sup>/hr, putting the assumed exposures at the low end of the Hughson and Aitken range.

One reference that is cited in the NMP RA, (Anundi et al., *Int Arch Occup Environ Health*, 2000) is under-utilized. Questionnaire data from professional graffiti removers reported there provides information on use of PPE (most, but not all, participants reported using gloves) and exposure to body parts other than hands (most participants reported splash exposures to face and body as well as hands).

Use of gloves, however, cannot be automatically assumed effective. Rawson et al., (*Ann Occup Hyg*, 2005) studied glove related exposure using a fluorescent tracer and demonstrated that naive glove use can lead to increased exposure. That study also used NMP as surrogate compound in a biomonitoring-based glove contamination study

Glove selection is glossed over in the NMP RA. A British study entitled *Protective glove selection for workers using NMP containing products – Graffiti removal* (HSL/2007/41) found that many glove types are ineffective against NMP. Stull et al. (*AIHAJ*, 2002) addressed glove

selection for paint strippers more generally (and would be relevant to the DCM RA if dermal exposure had been included).

The total surface area of both hands of an 80 kg worker was assumed to be 840 cm<sup>2</sup>. In contrast the surface area of both hands of an 80 kg residential user was assumed to be 980 cm<sup>2</sup>. No explanation for the difference was provided.

**Question 4-2:** *Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models or information that should be considered by the Agency for improving its assessment of the consumer dermal exposure, including specific citations (if available) of data sources characterizing dermal exposures in a residential setting. As part of the review, please comment on the strengths and weaknesses of the evaluation and the choice of assumptions/input parameters for generating estimates of the NMP's dermal exposure.*

In the consumer dermal exposure assessment, both conservative and non-conservative assumptions were made. Conservative assumptions include no use of gloves (although note caveat above), 100 percent absorption of deposited liquid and an adhering skin load of 33 mg/cm<sup>2</sup> of stripper. The stripper was plausibly considered to contain variable fractions of NMP. Non conservative assumptions include exposure of hands only, stripper contact with only 50 percent of hand surface area and only 1 exposure event per day. Task durations were also unrealistically short in simulations presented in PBPK model testing.

**Question 4-3:** *Please comment on the assumptions used by the Agency regarding film thickness for the assessment, including any additional data on film thickness with which to assess dermal exposure to NMP for both consumers and workers.*

Assumed film thicknesses used in the consumer and worker scenarios are not consistent. The consumer assessment assumes a film thickness of 0.03 cm (corresponding to 33 mg/cm<sup>2</sup> at s.g. = 1.1) based on what is apparently a minimally documented guess. This value is not sufficiently grounded to merit inclusion in anything other than a crude screening assessment. The consumer assessment (Appendix D, p. 143) dismisses skin adherence factors available in the Exposure Factors Handbook (EFH) as inappropriate, even though values from that source are utilized in the worker scenarios.

The adherence ranges cited in the EFH were generated in studies in which volunteers first wiped hands with an oil-soaked cloth and then briefly with a dry cloth [30 sec contact with a saturated cloth with or without a 5 sec dry cloth wipe-off gave means of 0.5-2.1 mg/cm<sup>2</sup>]. Skin loads were estimated from oil mass loss and/or gain. (Additional results from immersion studies were available, but not used in the NMP RA. "Immersion" [i.e., 10 sec immersion with 30 sec drainage, with or without a 15 sec dry cloth wipe] gave means of 1.3-10.3 mg/cm<sup>2</sup>). The worker assessment cites the EFH correctly, but the EFH cites the original work incorrectly. Only three substances (mineral, cooking and bath oils) were utilized. Three other liquids were considered, but ultimately not utilized due to concerns over evaporative loss.

Potential data sources for adherence to skin not cited in the NMP RA include:

- Gujral et al., (*Risk Analysis*, 2011) reported adherence of water post immersion as 2-7 μL/cm<sup>2</sup> (2-7 mg/cm<sup>2</sup>) on multiple skin surfaces.
- Gorman-Ng et al., (*Ann Occup Hyg*, 2013) reported adherence of water/glycerol mixtures post

immersion at geometric means 3-24 mg/cm<sup>2</sup>. Gorman-Ng also found increasing skin load with increasing viscosity.

**Question 8-1:** Please review the model and comment on the Poet et al. (2010) analysis as well as EPA's evaluation of the revised model. Please comment on whether the model is clearly and transparently described and technically and scientifically adequate for supporting OPPT's workplan risk assessment for NMP-based paint strippers. Specifically, please address the structure of the PBPK model, parameter calibration and model predictions of the available in vivo data.

The PBPK model code is very poorly annotated and hard to read. A significant flaw is the lack of a glossary of variable names. In addition naming conventions are often counter intuitive (e.g., body compartment "volumes" have labels starting with V, but are actually dimensionless mass fractions rather than volumes). Many changes have been made in the code since results were produced for the Poet et al. (*Toxicol Sci*, 2010) publication, either because claimed results could not be reproduced or because particular bits of logic in the code were judged to be incorrect when reviewed by EPA or its contractors. The model appears to very much be a work in progress rather than a well-established and vetted code. While apparently good fits to some sets of data have been presented, fitting of complex multivariate models to data can often be achieved via compensating errors. Given the proclivity of EPA personnel to recycle analyses, setting the standard for transparency and reproducibility of PBPK models this low at this early stage of the current TSCA risk assessment initiative would constitute a very poor precedent.

I have particular reservations about the quality of the code with respect to dermal exposure scenarios. The code treats skin as a CSTR. This is generally an inferior approach (see Norman et al., *Toxicol Sci*, 2008). The original Poet et al. version (*Toxicol Sci*, 2010) was calibrated using human dermal exposure from vapor only (Bader et al., 2008) and then tested against additional human vapor exposure data (Akesson and Paulsson, 1997; Xiaofei et al., 2000). The modified version has been tested against the Payan et al. (*Drug Met Disp*, 2003) rat neat dermal exposure data. Neither version of the model appears to have been tested against human liquid solution exposure data. Also, the biomarker results for Xiaofei et al.'s subject D are clearly badly underpredicted by the model, which might be an indication of significant dermal exposure to that individual.

In the consumer exposure scenarios described in graphical form in tab #2 (PBPK Exposure Time Course) of EPA-HQ-OPPT-2012-0725-0058, clear differences in predicted plasma concentration of NMP are evident between consumers wearing gloves and those not wearing gloves. In addition, plasma levels increase and decrease rapidly, i.e., reach C<sub>max</sub> in 15 minutes or less and return to baseline in a similar time frame. This outcome seems implausible. Akrill et al. (*Toxicol Ltrs*, 2002) immersed volunteer's hands in 15 percent solutions of NMP for 15 minutes. Urinary 5-HNMP did not reach C<sub>max</sub> until 8-10 hrs after exposure. Urinary excretion of 5-HNMP closely resembled the pattern observed by Akesson and Jonsson (*Scand J Work Environ Health*, 2000) following 8 hrs vapor phase exposure to 10 mg/m<sup>3</sup> of NMP. Akesson and Paulsson (*Occup Environ Med*, 1997) found that urinary NMP tracks plasma NMP and Akesson and Jonsson found that urine 5-HNMP tracks plasma 5-HNMP. It is likely therefore that Akrill et al.'s volunteers experienced elevated plasma levels of NMP much longer than predicted in the scenarios in EPA-HQ-OPPT-2012-0725-0058. The PBPK code should be tested against the Akrill et al. data. Significant storage of NMP in the skin is very plausible, especially when

administered in aqueous solution. NMP is hygroscopic and skin swelling that is sometimes observed subsequent to use could involve excess water retention in the epidermis or dermis. Akiril et al. (p. 202) specifically state that the probable explanation for their observed result is that “NMP absorbed into the skin during the immersion was being released slowly into the body over the following 8 h.” Residual binding of NMP in skin was also observed in the rats used in Payan et al.’s (2003) *in vivo* experiments.

The following comments are based on code provided in the Quality Assurance Assessment (QAA; as provided in EPA-HQ-OPPT-2012-0725-0055).

The skin clearance rate in a single-compartment CSTR model of skin can be estimated as

$$\frac{\text{Blood flow to skin [L/h]}}{\text{skin mass [kg] skin-blood partition coefficient [L/kg]}}$$

Using values I think are used in the modified Poet et al. model, I calculate this quantity to be roughly 60/h or 1/min. This means the average residence time in the skin would be 1 minute, which is too short.

Inputs are not provided in a systematic manner for all the scenarios tested. Initial values of some variables are apparently set to zero or near zero and then overwritten as necessary. In other cases non-zero values are embedded in the code. In the pregnant human model (QAA p. 30), VSKC is set to 0.19, which is the rat value rather than the human value. It is not possible to determine whether appropriate values were in fact used in test simulations presented graphically.

The initial NMP challenge concentration in patch exposure scenarios may be adjusted by multiplying the original concentration by the fraction not absorbed by the patch (QAA, p. 39). This is only logical if the NMP is in solution and is selectively absorbed by the patch. If the patch contains pure NMP or if both the NMP and the vehicle are drawn into the patch in proportionate amounts, this makes no sense, as the external thermodynamic driving force would not change.

Calculation of CSURF (QAA, p. 39) involves adjustment of the liquid concentration by subtraction of the amount that has already been absorbed divided by the vehicle volume. This assumes constant vehicle volume, which is a generally poor assumption.

Assumption that skin washing removes NMP in the skin, as opposed to on the skin, is not well justified (QAA p. 63). There is no evidence in the literature that material that has been absorbed into the skin is readily removed by normal washing procedures.

Assumption that dermal absorption of vapor occurs only in unclothed skin is arbitrary and not well supported.

### **Questions on the Risk Assessment**

***Question 9-5:*** Please comment on whether the risk assessment document has adequately described the uncertainties and data limitations in the methodology used to assess risks to allow the EPA to reduce risks to human health from NMP. Please comment on whether this information is presented in a transparent manner.

EPA has chosen to address uncertainty by considering alternative scenarios and varying point estimates for selected variables while others are held constant across all scenarios. This approach cannot capture the full range of uncertainty inherent in the risk assessment. A probabilistic approach could potentially (if well-conducted) prove much more informative.

## Dr. Stephen Pruett

The NMP risk assessment document is well written and addresses appropriate issues within the stated scope of the assessment. However, there are some issues that, if addressed, could improve the document.

The literature review in the NMP Risk Assessment Document appears to have some gaps with regard to references cited. Table 1 lists references that seem particularly relevant to this risk assessment that were revealed in a PubMed search but were not cited in the document. The search was conducted on November 8, 2013 using the search term, “N-methylpyrrolidone”. This search yielded 200 references. The references listed in Table 1 seem important to the current risk assessment document, but they were not cited in the document. It should be pointed out that it is rare that a search for a highly used chemical in PubMed yields as few as 200 references. For a variety of reasons, not all of these references are relevant, but it should be possible, without an excessive amount of time or effort to review the title and abstract of all of them and to determine quickly which ones might benefit this risk assessment document.

**Table 1. Apparently relevant references not cited in the NMP risk assessment document.**

– Sitarek	2012 (Reproductive effects) (Sitarek, <i>et al.</i> , 2012)
– Thakaberry	2013 (No effects reported-used as drug vehicle) (Thackaberry, <i>et al.</i> , 2013)
– Wang	2012 (No toxic effects-vehicle for anti-psychotic) (Wang, <i>et al.</i> , 2012)
– Argikar	2011 (No toxic effects-vehicle for pharmaceutical agents) (Argikar, <i>et al.</i> , 2011)
– Jouyban	2010 (Review of pharmaceutical uses) (Jouyban, <i>et al.</i> , 2010)
– Suzuki	2009 (Human exposure-urinary metabolites) (Suzuki, <i>et al.</i> , 2009)
– Nishimura	2009 (Worker health-no effect) (Nishimura, <i>et al.</i> , 2009)
– van Thriel	2007 (Chemosensory effects-but not others) (van Thriel, <i>et al.</i> , 2007)
– Ruble	2006 (No effect hematol/clin chem in dogs) (Ruble, <i>et al.</i> , 2006)
– Dudeck	2006 (No effect-cardiovascular) (Dudeck, <i>et al.</i> , 2006)
– Payan	2002 (Metabolism and excretion, rats) (Payan, <i>et al.</i> , 2002)
– Malley	2001 (No adverse effects on blood parameters) (Malley, <i>et al.</i> , 2001)



These references were selected because they were published by well known investigators in this field, were published in well-respected journals in this field, and/or their titles and abstracts indicated they were particularly relevant to the present risk assessment. One of the observations in some of these papers is that NMP was not found to be toxic or was (based on references cited in the article) assumed to be relatively non-toxic and acceptable as a vehicle for drugs that were under study. This is not mentioned in the risk assessment document, and this raises a concern that references cited in the document might have been selected in a manner that primarily identified studies showing toxic effects. It is certainly possible that some of the references in Table 1 were not cited because they failed to meet usability criteria, but there is no way to determine if this was the case on the basis of the information in the document. The appearance of objectivity of the document would be enhanced if the basis for selection of references was explained and if references that indicate little or uncertain risk of toxicity from NMP could be cited and an explanation provided regarding how these results were integrated into the risk assessment or the reason the results were not regarded to be reliable or useful.

The first paper listed in Table 1 is one that does report a toxic effect and it is one of a series of papers by the same author (Sitarek and Kilanowicz, 2006; Sitarek and Stetkiewicz, 2008; Sitarek, *et al.*, 2012) that report reproductive toxicity, but none of these papers are cited in this risk assessment document, even though reproductive and developmental toxicity are considered in the document. Again, there may be good reasons for excluding these papers, but the risk assessment document would be improved if these reasons were explained or if these papers were included in the assessment.

Although it seems appropriate to include in the scenarios evaluated some in which users did not follow safety instructions, it would be useful to clearly state which scenarios would not occur or would be unlikely to occur if recommended safety precautions were taken by consumers or workers in commercial establishments. This may also serve to highlight any problems that may exist with regard to precautionary statements on package labeling. On a related issue, information on the degree of compliance of consumers with manufacturer instructions is needed; a more detailed description of the findings of Riley, 1994 and Abt, 1992, which are cited in the document, may clarify the extent to which the user scenarios correspond to real world compliance. The role of human behavior in responding to irritating substances by increasing ventilation, leaving the area, or other actions does not seem to have been incorporated in extreme exposure scenarios or models. A concern of this type was noted in the NMP Producers Group Attachment B, and it would seem to be a valid concern.

In fact, the three considerations issues mentioned above seem interrelated and could be addressed together: a) Identifying which scenarios depict greater exposure than would occur in individuals who comply with manufacturer's safety instructions; b) Developing an evidence based estimate of the percentage of consumers who comply (or not) with safety instructions; c) Developing an evidence based estimate of the extent to which aversive characteristics of NMP limit exposures in situations in which compliance with safety instructions is incomplete.

Currently available data may not be sufficient to provide definite answers to b) and c). Perhaps existing publications, government studies, and industry studies could be re-examined with this in mind and evidence may be identified that would allow quantitative estimates. In any case, a discussion of these interrelated issues and whether or not they could be accounted for in the exposure modeling scenarios would enhance the document. If they cannot be accounted for using currently available data, it would seem appropriate to state this and to indicate that it may increase the uncertainty in this risk assessment.

A strength of the document is that the default assumptions are generally clearly stated and identified as assumptions. However, there are a few which may be worth additional consideration. For example, “Workers may have potential risks of concern from dermal exposure when no gloves are worn.” It was not clear that a thorough search indicated that there is no evidence-based information on the percentage of workers who do not wear gloves while working with NMP or on the percentage of time working with NMP when average workers do not wear gloves. A paper that was not cited in the risk assessment document (Stull, *et al.*, 2002) indicates gloves are effective in preventing NMP exposure, but not exposure to DCE and some other compounds used in paint strippers. References cited in this paper may include studies in which some estimate of the percentage of workers wearing gloves, and citation of this paper and a statement regarding the availability (or not) of such information in it might improve the risk assessment document.

Another default assumption is that “Consumers may have potential risks of concern from dermal exposure assuming appropriate gloves are not worn.” This is a reasonable assumption, but specific data on lack of compliance would be useful. Such data may not be available for NMP, but there have been a number of studies in academic journals as well as government or industry reports indicating that compliance with personal protective measures among both workers and consumers tends to be low. A summary of this literature could be used to strengthen this assumption and provide a more evidence-based document.

Another default assumption is stated as follows, “Consumers may have potential risks of concern from inhalation exposure (although of lower concern than from dermal exposure) if exposed for more than 4 hours at lower ventilation rates”. This is reasonable, but exposure and low ventilation rates should yield some degree of aversion to the odor or some degree of irritation which would motivate the consumer to limit his/her duration of exposure. This has been mentioned already as an issue that has not been fully addressed, and it is particularly relevant in the case of this assumption and may justify appropriate qualifying statements.

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