OPPT Methylene Chloride (DCM) 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 assessment provides a clear and logical summary of EPA's analysis. Please provide specific suggestions for improving the document.

The document is a fairly thorough and careful treatment of the potential exposures and risks presented by the paint stripping scenario involving DCM. It 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 well conducted and recent cancer and non-cancer potency derivations. 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. Thus, the planning and presentation are positive attributes. However, there are several areas which are unclear or incomplete.

The scoping phase needs more description of the overall objectives. The focus on paint stripping suggests that EPA is seeking to identify the single highest risk activity and leave aside all other activities; however, there may be other uses that are also associated with elevated risk. For example, the volume of DCM going into adhesives is greater than paint stripping (Table 2-4) and there is substantial potential for public exposure to adhesives. The level of risk associated with such secondary exposures is unclear but this becomes a natural question when the screening level analysis of the highest exposure (paint stripping) triggers health concerns. Thus, it is unclear whether EPA endeavors at some point to identify all high risk uses of DCM and how the current analysis would fit into that larger purpose.

Another major point is the exclusion of dermal exposure in spite of the assumption that gloves will not be worn. Greater justification is needed to exclude a DCM pathway when the use obviously involves extensive dermal contact. The scoping phase chose to focus on small stripping shops, which appears logical on the grounds that the high end exposure scenario may be more likely in such shops. However, it leaves open the question of whether DCM health concerns could exist is the larger shops and whether there is any reason to evaluate such shops.

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,(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). Appendix F provides

the rationale for exposure parameters based upon assumed stripping activities but it would be helpful if the stripping protocol was in the main document as a key part of the exposure assessment.

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

The background information provided is sufficient; no other documents are noted.

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 DCM workplace exposures, including specific citations (if available) of other data sources characterizing occupational inhalation exposures.

According to Table 3-3 the occupational exposure assessment relies heavily on pre-1997 data (only 1 or 2 occupations solely post-1997) while the change in occupational standards would suggest better engineering controls and lower workplace exposures after that date. Therefore, worker exposure and risk estimates may be biased high in Table 3-12. However, the emphasis on smaller shops which are theoretically less well regulated (less OSHA inspections?) might cause the pre- vs. post-1997 exposure differences less important. This can be further discussed in the uncertainty section (page 65) which now only says that exposure distributions may be declining.

It may be informative to separately list the individual occupational exposure studies by industry and years covered. While this would substantially expand Table 3-3, it may clarify how much pre- vs. post-1997 data are available. It may also be informative, if there are sufficient data, to provide summary statistics for the pre- vs. post-1997 data to determine whether DCM exposures are declining in particular industry sectors. For example, there are 5 studies in the furniture refinishing industry spanning the 1990-2007 period in Table 3-3. It may be possible to assess pre vs. post-1997 data across those 5 studies. Appendix Table E-1 provides OSHA monitoring data across a wide array of shops but the year associated with those measurements is not indicated. Appendix E text makes it clear that some shops are still exceeding OSHA standards well after 1997 although the levels appear to not be quite as high pre-1997. If a quantitative analysis of the air concentration trend is not possible, it would appear that one could at least use the information in Table 3-3 and Appendix E and in the underlying studies and reports to decrease the uncertainty associated with the use of Table 3-3 data (mostly pre-1997) for modern day workplace DCM exposures.

No other studies were identified which reported dermal uptake data for DCM in humans but this was not an exhaustive search on my part and its possible that data in humans or rodents may exist and be informative. The assumption in the draft risk assessment that dermal will be small relative to inhalation due to DCM volatility is likely correct but that doesn't mean that dermal exposure from paint stripping activities couldn't present a significant risk, especially where room ventilation curtails inhalation exposure and dermal becomes the main 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 in developing the exposure assumptions and estimates for the consumer use of DCM-based paint strippers and for the bystander/non-users (e.g., children, women of childbearing age). As part of the review, please 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 DCM air concentrations.

Exposure estimates in the residential scenario are based upon a model described on Pages 35-38. There are a number of uncertain parameters which needed estimation based upon stripping methodology, worker behavior, room dimensions, air flows and DCM amount applied. A state of the art protocol based upon label directions and surveys such as that reported by Riley et al. 1990 would be helpful to understand the different inputs and range of assumptions used in the base modeling and sensitivity analysis. For example, Appendix F states that it is unlikely that multiple segments of one piece of furniture would be worked on simultaneously which would suggest that multiple pieces of furniture would not be handled in one session. It is also assumed that a chest of drawers of 25 ft2 would represent an upper end of exposure. However, these are not well documented assumptions and the uncertainty regarding these and other paint stripping assumptions should be clearly stated. Perhaps the intention is that the bathtub scenario should represent the upper end of stripper exposure but that is not a normal stripping activity and is well known to be hazardous. Therefore, it may be worth considering a larger surface area or longer time sequence for the furniture scenario to simulate larger jobs or those involving more ornate or complex features. The assumption of only 33% release rate of DCM is justified based upon a 1994 USEPA document. Given the volatility of DCM this is a rather unexpected assumption and so should be more thoroughly explained than attributed to a passing reference. Where ever possible distributions or ranges for parameter values should be used to better address variability in the exposure scenario.

As described on Pages 33-34, there are limited chamber and residential DCM stripper data that, while not suitable for exposure assessment on their own, may be useful for ground truthing the modeling results. For example, the CPSC and USEPA datasets, while dated and the original data are not available, may still help remove some of the uncertainty associated with the residential exposure scenario. Further the van Veen 2002 DCM stripper exposure study has some utility. It appears that USEPA does not have any real reason to question the results from those studies. Therefore, USEPA should evaluate whether any aspect of the chamber and residential data could be used to check model results.

The Executive summary states that exposures to children are assessed. Yet there was no assessment of children's exposure in the document. Children are again mentioned with respect to the setting of AEGLs. More explicit consideration of child bystanders would be an improvement.

Some may feel that the warning properties of DCM or other paint strippers will alert the user to an irritating, odorous or otherwise unhealthy exposure and cause aversive behavior. Risk assessment cannot count on this as a rationale for exposure cessation as everyone's level of sensation, tolerance and fatiguing (dissipation of odor or irritation – some properties one can get

used to) differ. The fact that fatalities have been reported with DCM in bathtub applicators and other scenarios is an indication that warning properties aren't always sufficient to mitigate exposure before acute effects occur.

Question 4-1: Please comment on EPA's use of the acute PODs that were identified from the technical documents supporting the Cal EPA REL, SMAC and AEGL derivations. As part of the review, please provide your input on the appropriateness of the approach, including its underlying assumptions, strengths and weaknesses. Please provide any specific suggestions or recommendations for alternative approaches that should be considered by the Agency in characterizing the acute inhalation risks. Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.

The "context levels" approach is helpful to consider a range of acute endpoints of differing derivation and severity. However, it also leads to potential for conflicting and confusing results. Two acute inhalation criteria are presented for minimal (detection) level of effect – the California acute REL (14 mg/m^3) and the AEGL-1 (710 mg/m^3). The derivations are very different and should be compared and critiqued given the large difference between these values. The AEGL-1 is not used but the AEGL-2 is used for a different purpose (more dramatic health effect from acute exposure) so evidently USEPA places confidence in the AEGL derivations. Why should the California REL be so much lower than the AEGL-1 and why did USEPA choose the California REL for risk calculations?

USEPA chose to carry through two different PODs for acute risk evaluation (1 hr exposure), 842 mg/m^3 as a LOAEL from the California REL determination, and 350 mg/m^3 as a NOAEL from the SMAC determination. Without having looked at the derivation of these two values (Putz et al 1979 for the California LOAEL vs. Putz et al. 1979 and 5 other studies for the SMAC NOAEL), it would appear that the NOAEL is a more definitive POD because it actually defines the NOAEL rather than having to use an additional UF from a LOAEL (6x in the case of the Cal REL POD). Also, it seems unnecessary to carry two similar acute PODs through the calculations. Therefore, I would tend to choose the NOAEL-based POD derived by NAS for the SMAC but upon closer inspection USEPA might choose the LOAEL-based POD from California. In either case, it would be preferable to have a single acute POD. The HQ approach is reasonable for the AEGL-2 determination so that the simulated DCM exposures can be put into the context of more severe DCM effects.

Question 4-2: Please comment on EPA's choice of PODs and IUR for evaluating the non-cancer and cancer risks, respectively for chronic exposures to DCM-based paint strippers. As part of the review, provide your input on the appropriateness of the approach, including its underlying assumptions, strengths and weaknesses. Please provide any specific suggestions or recommendations for alternative approaches that should be considered by the Agency in characterizing the chronic inhalation risks to workers. Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.

The chronic non-cancer POD approach is confusing and needs clarification. Table 3-8 and Appendix H (Page 168) show that the RfC is based upon a cumulative UF of 30-fold. Yet the

MOE chosen by USEPA for evaluating the non-cancer POD from the RfC is only 10-fold. It appears that USEPA dropped the 3x data gap UF. The text related to this on page 56, first paragraph talks about the benchmark MOE for acute effects of >30 (why are acute effects mentioned in this section) and then goes on to describe an MOE of only 10 without describing why the MOE is not 30 to match the RfC UFs. Dropping the data gap UF seems incongruous with the statement on Page 48 that there is a very important data gap with respect to developmental neurotoxicity. The importance of this data gap is supported by DCM neurotoxicity in adult testing showing neurotransmitter effects. However, there is no discussion of the dose levels where DCM produced these effects. This would be useful information as one considers whether filling the data gap would substantially alter the acute or chronic PODs.

The RfC appears to be well constructed and is a recent derivation. It uses a total UF of 30-fold, which includes a database UF of three-fold. Thus the RfC POD and UFs appear to be a solid foundation for non-cancer chronic worker scenario risk evaluation. Similarly, the cancer IUR is a recent derivation on IRIS based upon liver and lung tumors in mice for which PBPK-based dosimetric adjustments were used and for which there is a mechanistic basis to use glutathione metabolism as a relevant internal dose metric. The toxicology assessment did not bring in the epidemiology or case reports which add to the body of knowledge regarding DCM-induced acute (a number of reports of acute overexposure and lethality – e.g., Mclsaac et al. 2013: *Am J Indust. Med* 56: 907–910) or chronic exposure (e.g., cancer epidemiology studies and summaries thereof).

Question 5-1: Please comment on the assumptions, strengths and weaknesses of the MOE and HQ approaches used to estimate the acute non-cancer risks to consumers of DCM-based products, including bystanders/non-users (e.g., children, women of childbearing age). Please also comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the acute risks.

Acute risks to consumers were estimated from acute toxicity values from California (REL), a value derived to protect astronauts (SMAC) and an AEGL meant to prevent disabling exposures (AEGL-2). As described above, the AEGL-1 is also in the running for acute POD or direct comparison value. The SMAC divided by an intra-human UF of 10 (MOE of 10 in the current context) may be the most robust of the 3 potentially useful values. Use of the AEGL-2 for consideration of more serious inhalation effects would appear to be reasonable with an HQ approach but it should be recognized that the DCM AEGL-2 does not have a factor for human variability on the basis that it is also not at a level of severity usually considered appropriate for AEGL-2 values. The AEGL-2 is 2000 ppm (1 hr), a high concentration relative to the OSHA 15 minute STEL which is only 125 ppm. That may be another HQ point of comparison for the acute assessment. Overall, the use of 60x from the CalREL POD and 10x from the SMAC appear to be reasonable MOE factors.

Question 5-2: Please comment on the assumptions, strengths and weaknesses of the MOE approach used to estimate the chronic non-cancer risks for workplace exposures. Please also comment on the selection of composite uncertainty factors that were used as benchmark MOEs to determine the chronic risks.

The use of the RfC as the non-cancer basis is reasonable and supported by PBPK modeling to go from the internal dose in rats which produced hepatic vacuolation to the corresponding internal dose in humans. As mentioned above, it would appear that the MOE factor should be 30 fold not 10-fold.

Question 5-3: Please comment on the assumptions, strengths and weaknesses of the cancer estimation risk approach used for the workplace exposures.

The cancer estimation procedures look appropriate and are based upon a robust cancer IUR in which PBPK modeling, multiple endpoints, internal dosimetry and an alternative assessment relying on external dose were all supportive of the derived IUR.

Question 5-4: 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 DCM. Please comment on whether this information is presented in a transparent manner.

The uncertainty discussion is very qualitative and does not provide a sense of whether a given uncertainty may tend to over or under predict risk. For certain issues it may be easy to tell that the uncertainty will tend to underpredict risk (e.g., no dermal exposure, no children's exposure, no cumulative exposure) or in other cases overpredict risk (250 days/year for 40 years may overpredict cancer risk – surveys of how long workers tend to stay in paint stripping would be useful information if available). It may be difficult to determine whether the neurodevelopment data gap in the DCM database will be a major source of risk underprediction but as a data gap mentioned both in the IRIS RfC assessment and currently, it seems incongruous that it is dropped from the MOE factors in this document. Another potential source of risk underprediction not characterized in the current document is the cumulative exposure from other uses of DCM around the home – this is likely to be minor as background indoor air concentrations of DCM are likely to be in the ppb range rather than the ppm concentrations associated with active furniture stripping but paying attention to cumulative risk is important in principle.

Finally, the DCM modeled predictions show that in some scenarios serious acute health effects are possible as concentrations above the AEGL-2 are predicted, suggesting that DCM-based paint stripper use is an inhalation hazard. DCM has been used as a paint stripper for many years. It would be relevant to bring into the discussion of risk any epidemiological or clinical case studies which document DCM workplace or consumer health effects and the approximate exposure levels involved. There is evidently a literature describing this which could provide important perspective on the acute risks associated with DCM use in strippers (see Mclsaac et al. 2013: *Am J Indust. Med* 56: 907–910). It would be good to characterize these events as industrial

accidents vs. exposures that can occur from routine practice to determine their relevance to the predictions made in the current residential modeling and worker assessments.

Tom Armstrong

Issue 1.

Question 1-1. As far as it goes, the report is clear and logical. However, the analysis of the exposure data and modeling need additional work.

Question 1-2. Additional detail on the background information is needed. See further comments under Issue 2 and 3. Several possibly relevant additional citations are included on the response to Question 2-1, response item 4.

Issue 2.

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 DCM workplace exposures, including specific citations (if available) of other data sources characterizing occupational inhalation exposures.

1. Reporting just the ranges of the data is not ideally informative as completed in the draft. Near Table 3-3, page 30, the draft DCM report states "EPA determined that the available datasets were not amenable to developing statistical distributions of all exposures in the specified industries." Only the number of studies and the reported range from low to high are given. Where multiple studies were available, Table 3-3 lumps them together, such as "Professional contractors, four studies 1990 to 1998, range short term exposures 130 to 14,100 mg/m^3", or "Furniture refinishing, four studies 1991 to 2007, range of TWAs 2.4 to 1,270 mg/m^3." There are several other categories where this composite range creation was not necessary and individual report data could have been show. Listing the data report by report would allow a better understanding than does the composite range. Without further information from the summarized studies, it is difficult to know how likely the upper end values are compared to statistical measures even limited to a mean or interquartile ranges or other simple statistic. Even the number of measurements in the range, when available, would be more informative than just the range. The analysis may be limited by the details in the reports, but without further discussion of the content of the data sources, this cannot be determined.
2. Citations for the sources of the data should be added to Table 3-3, even though cited in Table 3-4. Merging tables 3-3 and 3-4 could make the whole assessment easier to verify.
3. Using the high end of the range value to calculate a LADC does not seem ideal even as an upper end estimate, since it is not likely that every day's exposure for a lifetime would be at the top end of a range of exposures. Certainly, not all workers would experience this extreme. If there were only two measurements of exposure, the low and the high of the range, then logically the low must have been found one-half of the time and the high only the other half. This limitation should be mentioned in the uncertainty analysis for the exposure assessment. Perhaps for a risk assessment intended for more than screening

purposes, a probabilistic approach to the LADC estimation could be considered. As conducted, this upper end of range analysis is arguably a screening level assessment.

4. Given the OSHA PEL reduction in 1997, examination of differences in exposure before and after 1997 should be considered. In Table 3-3, there are a few industry categories with multiple studies where the time range covers before and after 1997. Giving the results study by study instead of aggregated would allow review of possible exposure changes over time.
5. The search strategy and search terms are not discussed. Thus, it is difficult to understand the depth of the search, although it seems to have located most of the relevant literature. For this peer review, only limited time was given to searching for additional sources of arguably relevant occupation data, but a few were found. Examples of possibly missed information include: (a) Estill, Cheryl Fairfield, and Amy Beasley Spencer. "Case study: Control of methylene chloride exposures during furniture stripping." *American Industrial Hygiene Association Journal* 57.1 (1996): 43-49 [Note: the data from this may be included and cited as a NIOSH report, though], (b) Hall, Ronald M., Kenneth F. Martinez, and Paul A. Jensen. "Control of Methylene Chloride—Furniture Stripping Dip Tank." *Applied Occupational and Environmental Hygiene* 10.3 (1995): 188-195 [Note: the data from this may be included and cited as a NIOSH report, though], (c) NIOSH Criteria Documents: Criteria for a Recommended Standard: Occupational Exposure to Methylene Chloride DHHS (NIOSH) Publication No. 76-138 (March 1976) [Note: dated information, but might have been mentioned], (d) http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-10.pdf [The IARC report cites paint stripping references not included in the draft DCM. Although not limited to paint stripping uses of DCM, the data from other industries may be of utility in a "read across" manner.]

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 in developing the exposure assumptions and estimates for the consumer use of DCM-based paint strippers and for the bystander/non-users (e.g., children, women of childbearing age). As part of the review, please 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 DCM air concentrations.

1. The Draft DCM report Appendix F, page 131, somewhat misleadingly misquotes Matthews 1989.

A. Matthews report does not give information to suggest they "determined experimentally that such an airflow could be estimated as the product of the room air velocity (in m/hr) and the entry/exit surface area (in m^2)." That information was not found in a reading of Matthews 1989. The concept is mostly correct, but incomplete in development and explanation. The interzonal airflow is ½ of the generation zone's assumed free surface area times the space's random air velocity. The discussion is not sufficiently detailed to follow the actual calculation. The impression, though, is the calculation failed to assume the airflow into and

out of the zone must balance, so only ½ of the flow can be directionally out of the source cloud. Figure F-6 shows the source cloud volume as 1 m^3. It is also not clear in the text if the modeling places the exposed individual within or outside of tis source cloud. However, page 158 states the user was in the source cloud during application and scraping.

B. Matthews 1989 does not give a "suggested value of 65 m/hr for air velocity" as the draft report states. Matthews reports values in cm/sec and 65 m/hr converts to 1.8 cm/sec. The closest to this found in Matthews 1989 is the lowest reported median velocity was 1.1 cm/sec in a bedroom with purposely limited activity. The DCM user activity would prevent such a quiescent condition low air velocity. For spaces with human activity, the more typical median values were 10.2 cm/sec or 365 m/hr. Exposure with more likely air velocity should also be developed, reported and discussed.

2. The concept of a "near field" zone developed for the bathtub stripping scenario also applies to the other scenarios. The US EPA MCCEM model assumes instantaneous complete mixing in each zone. [This reviewer could not install MCCEM on a current computer to verify this or even to read the model documentation, and is relying on personal use of MCCEM about 5 + years ago. The MCCEM install file may be outdated.] Industrial hygiene literature [Nicas, Mark. "Estimating exposure intensity in an imperfectly mixed room." *American Industrial Hygiene Association Journal* 57.6 (1996): 542-550.] shows the well mixed chamber assumption usually underestimates exposure when the worker is close to the emission source. This effect is most notable for brief tasks. MCCEM is not well-designed to handle this issue but could be rigged by using an artificially smaller space as a worker near field within the work room. Given this, the MCCEM results may be better represented as suitable for a screening level assessment.

3. There are a few additional questions about the exposure during DCM stripper application.

A. Is the exposure time during application set at a reasonable upper end value? Table F-3, page 128 suggests 2 minutes, but the basis for this is unclear. From a sentence on page 67, is the source of the 2 minute application assumption US EPA 1994b?

B. Is the release fraction of 0.33 correct for DCM brush on application? DCM is a high volatility solvent. This is based on USEPA (1994b) report data. That implies 0.67 remains in the removed paint film and does not contribute to air concentrations. The report states (page 132) "It was further assumed that the scrapings were removed from the house as soon as scraping was completed for the last segment." Is the 0.33 the fraction estimated as released during the 2 minute application, with the additional 0.67 lost during the 15-minute wait period and a 4 minute scraping period? If so, this could be clarified on page 127 or elsewhere in the report.

C. It appears the potential for the user to serially apply stripper to multiple furniture pieces was not considered in an upper end estimate. This is likely less prevalent than a single piece application, but should be considered and discussed.

4. The assessment of exposures to bystanders and to the consumer engaged in the activities while out of the work zone appear reasonable. The input parameter choices seem reasonable. An appendix showing the actual inputs to and set up of the MCCEM model (such as via screen captures) for one of the scenarios could be helpful.

5. On page 34, the draft DCM risk assessment dismisses a 1994 EPA report on DCM since "the values for the required exposure factors, (e.g., room/house volume, airflow rates, and surface area of object) do not reflect the range of possible residential values," but states "the study was useful, however, in determining product application rates (i.e., in g/ft^2 and g/min) and in estimating the fraction of applied chemical mass that ultimately was released to the indoor air, as described in more detail in Appendix F, F-1." It would seem the 1994 EPA report's air concentration results should nevertheless be compared to the current modeling results. The same concern applies to studies mentioned at the top of page 35 (EC, 2004, van Veen et al 2002). The argument of lack of raw data and thus inability to verify the results can be said of most published reports. It seems the data from these reports should be summarized and discussed instead of being completely dismissed. It may be true that the EC (2004) study "exposure scenario assessed did not represent well use patterns in the US." However, use patterns in the USA are not homogeneous, and the EC results may help enlighten us on the range of possibilities in the USA.

6. Page 12 of the draft DCM RA states "…the assessment covered exposure scenarios via inhalation and did not address dermal exposures because this route of exposure is not expected to be as significant as compared to inhalation." This is likely correct. However, an estimate of the dermal contribution to total dose for at least one scenario would add more credibility than this not well-supported dismissive statement.

Issue 5.
The following comment may overlap several of the questions, but perhaps applies most to Question 5-3. For DCM, multiple human epidemiology investigations have been published. These seem to have received little attention and discussion in the draft DCM risk assessment. Although there has been controversy of such issues as the power in some of the epidemiology reports, they should be examined for the potential to bound the risks estimated in the draft and then discussed in the draft.

Question 5-4. See the response to 2-1 and 3-1. The discussion of the uncertainties and limitations is good as far as it goes, and it does cover the main issues adequately. The discussion is solely qualitative though, and does not help develop a quantitative understanding of how reliable the upper end risk projections may be. A table listing all the identified uncertainties with an indication of their direction and possibly a qualitative statement such as minor, moderate or major contributor to overall uncertainty could be considered. The uncertainty analysis should focus on the epistemic uncertainty. The sensitivity analyses cover the aleatory aspects. The limitations of the occupational data analysis are not fully discussed in the uncertainty analysis.

Frank Barile

1. Provide input on:

A. Appropriateness of the approach
B. Assumptions, strengths, weaknesses
C. Alternative approaches
D. Other studies and endpoints

2. DCM Charge Questions

Questions on Non-Cancer Hazard Assessment

***Question 4-1*:** Please comment on EPA's use of the acute PODs that were identified from the technical documents supporting the Cal EPA REL, SMAC and AEGL derivations. As part of the review, please provide your input on the appropriateness of the approach, including its underlying assumptions, strengths and weaknesses. Please provide any specific suggestions or recommendations for alternative approaches that should be considered by the Agency in characterizing the acute inhalation risks. Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.

3. DCM Charge Questions

Questions on Non-Cancer Hazard Assessment

***Question 4-2*:** Please comment on EPA's choice of PODs and IUR for evaluating the non-cancer and cancer risks, respectively for chronic exposures to DCM-based paint strippers. As part of the review, provide your input on the appropriateness of the approach, including its underlying assumptions, strengths and weaknesses. Please provide any specific suggestions or recommendations for alternative approaches that should be considered by the Agency in characterizing the chronic inhalation risks to workers. Please provide relevant data or documentation and rationale for including other studies and endpoints for consideration.

4. Overview of peer review panel:

A. General comments on DCM use
B. DCM use with small contractors:
    - Less than 10 employees
    - Small projects
    - Non-cancer hazard assessment: Highest exposure to users, less to non-users and "bystanders"
    - 1997 PEL lowered from 500 ppm to 25 ppm
    - No ecological impact
    - Industrial paint strippers contain 70-90% DCM;
    - Household P.S. contain 60-80% DCM

5. Acute inhalation risks

A. Consumer paint stripper scenarios and respective bystanders
B. Include small commercial shops, less than 10 workers
C. Small markets and industrial use settings not included in RA; better monitored
D. Use mostly aerosols and polyurethane foams

Risks are greatest when applied as spray-on and brush-on applications, no masks, no gloves;

Margin of Exposure (MOE) estimates increase for inhalation and dermal exposure;

6. Acute inhalation risks (Continued)

A. DCM is a "probable human carcinogen"
B. Acute Inhalation risks exist for non-cancer effects
C. Calculated potential risks based on Margin of Exposure (MOE) estimates. MOEs ranged between 0.2 and 4 (benchmark MOEs = 10 or 60 depending on selected hazard value)

7. Acute inhalation risks (Continued)

Acute non-cancer hazard exists for:

A. immunosuppressant, CNS toxicity, infectious through association
B. Otherwise, DCM has low hazard accumulation, low bioconcentration, and low hazard to aquatic organisms

8. Chronic inhalation risks

Cancer risks calculated for chronic hazard only

A. Non-cancer Chronic exposure risks include:
   - Liver toxicity, cancer (liver and lung);
   - Brush-on & spray-on applications

9. Hazard ID and Dose-response

Acute

A. Most of the toxicity due to DCM is related to metabolism to CO, COHb
B. CNS, lung, heart toxicity is not dose-dependent
C. CNS toxicity related to CO poisoning…up to 200 ppm
D. Neurodevelopmental toxicity most relevant

Chronic

A. Neurological toxicity, 70-100 ppm
B. Rodent studies:
   - Cancer - lung, liver, mammary 1000-2000 ppm
   - Liver – up to 2000 ppm

10. Key sources of uncertainty:

Acute PODs

A. Screening level assessments are not robust
B. Kinetics
    - Rapidly absorbed by inhalation, 40-60%
    - rapidly distributed
    - Half-life = 40
    - Metabolism: liver, CO, CO_2, methHb, fornaldehyde, formic acid

11. Acute PODs and acute toxic effects

A. CNS: due to COHb production; interaction with neuronal membranes;
    a. 200 ppm X 4-8 hrs
    b. Neurobehavioral, neuropsychological
    c. Neurotransmitters are affected: GABA, GLU, Ach
B. Lack of developmental studies
C. Lack of gestational DCM exposure studies

12. Acute PODs and acute toxic effects (Continued)

A. Highest concentrations in ship, aircraft, flooring, automotive industries
B. Of 13 fatalities with bathtub refinishers, blood [DCM] = 18-223 mg/L
C. Equivalent to 93K to155K ppm vapor phase in bathtub or 5100-8500 ppm in bathroom
D. IDLH (NIOSH) = 2300 ppm

13. Chronic PODs and chronic toxic effects

A. Chronic studies
    i. Few studies available; most studies are rodent
    ii. Chronic human LL DCM exposures are lacking
    iii. Of available human studies, limited by sample size and systematic dose-response exposures;
B. Toxicity results in relation to ambient concentrations…

i. Neurological toxicity, 70-100 ppm
ii. Rodent studies: limited to 2-yr carcinogenicity studies
iii. Cancer - lung, liver, mammary 1000-2000 ppm
iv. Liver – up to 2000 ppm
i. 1000 ppm X 6 hr/day
ii. Renal tubular degeneration, testicular and ovarian atrophy (2000-4000 ppm)
iii. Conclusions: “likely carcinogenic in humans” based on mutagencity and gentoxicity studies

14. Data gaps for occupational exposures

A. Potential developmental neurotoxicity with chronic low-dose DCM
B. Is data representative?

C. Questionable number of facilities, sites, residences
D. Sampling pools vary
E. Work practices and precautions are variable
F. Preventive measures are not adequately documented
G. Number of establishments and number of employees may be overestimated (e.g. not all employees working in a job site that use DCM will likely be exposed to the chemical)
H. Age of data (most studies performed in 1990s); cutoff year appears to be 1997

15. Data gaps for occupational exposures (continued)

A. Product use; e.g. art restoration v. bathtub refinishing or surface coating
B. Use of other products during DCM use
C. Room of use v. ROH (rest of house)
D. Other assumptions; e.g. LADC assumes 250 days/yr X 40 yr:
   - Overestimate number of potential establishments, exposed employees (e.g., not all employees working in a job site that uses DCM will likely be exposed to the chemical
   - Professional users (contractors) vs. consumers (household)

16. Data gaps in human health toxicity studies

- Rodent studies: no significant developmental or reproductive effects concluded from 2-yr rodent studies
- Some effects on fetal b.w.
- Some neurobehavioral, pulmonary effects (pneumonia)
- Results from rodent cancer studies concluded that DCM is "likely to be carcinogenic in humans"
  – Based on inhalation studies & dose-response
  – Lung, liver, mammary
  – *In vitro* mutagenicity studies
- Mechanism of carcinogenicity
  – Mutagenic
  – Saturation of CYP 2E1, then switch to GST-pathway
  – Formation of intermediate metabolites react with DNA; i.e. GST-pathway metabolites
  – Chromosomal aberrations in lung, blood dyskrasias
- AEGL-1, AEGL-2 based on human cases; AEGL-3 based on animal studies

17. Other considerations for occupational exposures

A. How are HEC (human equivalent concentrations) calculated (mg/m^3)?
B. Alternate equivalent calculation, HETC (human equivalent toxic concentration) calculated from LD50s and Vd (volume of distribution); (Barile, 2013; Yang *et a*l., 2002;)
C. High variability of non-user exposure
D. Attention to spray application in workshop or brush application in bathroom

18. Summary of answers to charge questions

***Question 4-1*:** Questions on Non-Cancer Hazard

Assessment (see above)

A. Approach is appropriate.
B. Assumptions are based on kinetic modeling and on comparisons of ppm concentrations. However, ppm cannot be adequately interpreted throughout various studies.
C. Ppm concentrations are suitable for estimating acute inhalation risks. However, blood [DCM] concentrations are not comparable and are mostly lacking in human case studies.
D. Examination of other studies and endpoints for consideration are necessary so that a more suitable rationale can be constructed for estimating risk for acute inhalation toxicity.

19. Summary of answers to charge questions (Continued)

Question 4-2: Questions on Non-cancer Hazard Assessment

A. EPA's choice of PODs and IUR for evaluating the non-cancer risks are appropriate. However, levels are limited by the availability of the data. As stated above, most of the human non-cancer effects are based on case studies and observations at the workplace sites. Consequently, the toxic effects are probably accurate as far as the consistency of the observations are documented. Calculations of the PODs are based on individual blood [DCM] levels and, consequently, are of limited value. That is, the calculations are scientifically valid but the blood levels are questionable;
B. Cancer risks for chronic exposures to DCM-based paint strippers are well documented through rodent studies and cell based tests (genotoxicity tests). However, human cancers have not been adequately confirmed. In particular, DCM cancer risks are valid due to cell based and rodent studies. Human risks are questionable mostly because of extrapolation of MOE.
C. Approach is based on PBPK modeling and is appropriate. Alternative approaches to characterize the chronic inhalation risks to workers will need more rodent studies, and better follow-up on human case sites.
D. Relevant data, documentation and rationale for including other studies and endpoints for consideration are based on following references.
E. Metabolic studies in mice may be overestimating toxicity. For instance, mice over-express $CypP_{450}$ enzymes and may over-produce reactive metabolites, which is not observed in other species.
F. Mice demonstrate saturation of $CypP_{450}$, then shift to GST metabolic pathway. These metabolites react with DNA, i.e. GST-pathway metabolites. However, PBPK model may already account for over-expression of metabolism in mice. Risk assessment and expanded PBPK models may need to be developed.
G. Major consideration: metabolic activity of mice may not adequately represent a model toxic profile. Mice, among other rodents, are more sensitive to DCM based on higher levels of CypP450 enzyme activity. Consequently, at moderate to high DCM levels, Cyp

2E1 is saturated, resulting in shifting of metabolic pathway to GST-based metabolism. GST metabolites readily react with DNA in a variety of organs, particularly the liver.

H. Chromosomal aberrations also appear in lung, and red blood cells demonstrate malformations, as a result of reaction of GST metabolites with DNA of the respective organs.

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Anneclaire De Roos

Document, Overall

The Executive Summary should be rewritten. I have several comments about this section:
-It doesn't contain any information on the toxicological studies/hazard identification before the last 2 bullet points when neurotoxicity is mentioned. The nature of the health endpoints should be explained in a paragraph earlier on.

-The 4th paragraph on page 13 starts by saying how cancer risks were calculated, but then doesn't go on to say what the results were.

-The 5th paragraph on page 13 says that the residential (consumer) inhalation exposure modeling was "based on workplace air monitoring data". This is not completely true as the EPA 1994 study used for emissions modeling was a study of exposure to consumer products by volunteers.

-The sentence starting, "In conclusion,…" mentions that there were only exposures of concern for non-cancer risks. This should say "cancer and noncancer risks".

Occupational Inhalation Exposure

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 current presentation. For example, in the appendix (page 104) one of the studies is described of consumer exposure levels (EPA 1990), but this is listed in Table 3-3 under 'Professional contractors'. I agree that this study should be in the table, but please provide

individual study data and citations. The EPA 1994 study (by MRI) is described in the appendix (page 105), but it is not clearly listed in Table 3-3. This study provided 8-hour TWAs, which aren't shown; however, during the phone meeting on 12/13/13, an EPA staff member explained that the 8-hour TWA from this study was not suitable for comparison to the other 8-hour TWAs listed.

If listing the individual studies in Table 3-3 is too much for the main document, then a full table in the appendix (in addition to the descriptive text) and a summary table in the main document would suffice.

Consumer Inhalation Exposure

The amount of detail in the appendix for the consumer inhalation exposure modeling is good. This document provides a much more detailed explanation of the process and assumptions than in the NMP document.

Because neurotoxicity is a concern for DCM, consideration should be given to non-user exposure to children. Children are likely to have different activity patterns within the house than adults and would also be closer to the ground, which may affect inhalation exposure levels.
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% 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.

Hazard Identification and Dose Response Assessment

CNS depression was one of the main toxic endpoints considered, but the toxicology studies supporting this are not presented in Appendix G (Human Health Toxicity Summary).

Risk Assessment

The risk assessment should be based on the AEGL-1 value rather than the AEGL-2. The fact that light-headedness and difficulties in enunciation happen at the AEGL-1 level is of concern, as this might impair judgment for good work practices.

Ronald Hood

I have no response to most of the charge questions regarding this review draft. However, I do have a response to **Question 5-4:** 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 DCM. Please comment on whether this information is presented in a transparent manner.

Reviewer's response:

The DCM draft risk assessment states the following: "The potential for developmental neurotoxicity occurring at lower exposures to DCM represents a very important data gap." However, it is unclear if the risk assessment took this data gap into account in determining PODs, calculating MOEs, etc.

John Kissel

General Question on the Risk Assessment Document

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.*

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 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 DCM workplace exposures, including specific citations (if available) of other data sources characterizing occupational inhalation exposures.*

The exposure assessment perfunctorily dismisses dermal exposure to DCM. Due to the volatility of DCM, dermal exposure is often a minor contributor to aggregate dose when compared to inhalation exposure. However, solvents such as DCM do penetrate the skin rapidly under occluded conditions, so some assessment should be provided. This should include at least screening level consideration of potential dermal dosing when respiratory protection is provided.

Questions on the Risk Assessment

Question 5-4: *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 DCM. 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.

Stephen Pruett

The DCM 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 selection of workers in small shops and consumers for this assessment is not unreasonable, nor are the assumptions on which it is based. However, a major reference used to describe the behavior of consumers and workers in small shops does not compare behavior at larger operations and is based on a survey that relies on the memory of the worker/consumer (Riley, *et al.*, 2001). The deficiencies of this study are noted in the risk assessment document, but it is one of the few papers that may be seen as supporting the assumption that consumers and workers in small shops are exposed to higher concentrations of DCM than workers at larger shops. The authors of the current document have presented a thorough report on exposure levels of DCM in paint stripping uses. A thorough segregation of these levels by small shop/consumer as compared to large operation, and the addition of additional exposure data from large operations, could provide a stronger case to justify the focus of this risk assessment document.

It should also be noted that an important aspect of worker/consumer behavior is not represented in the models of exposure developed in this document. Specifically, the response of people to high concentrations of volatile agents, which tend to be aversive, even if not highly irritating or painful, has not been considered. It seems reasonable to assume a worst case scenario in which people do not react by moving away from high concentrations of DCM, but this should be adequately considered and discussed. At present, this issue is simply not considered in the modeling process. This could perhaps be addressed by a more thorough description of the circumstances under which fatalities caused by DCM exposure occurred. For example, it is possible that workers using the compound in bathtubs were rapidly rendered unconscious by placing their head below the top of the tub (an area in which the concentration of DCM is presumably much higher than in the remainder of the room). If so, the normal response to aversive stimulus may not have been possible. However, if these persons were slowly overcome while inhaling air above the top of the tub, this would suggest that the aversive stimulus was not sufficient to cause some individuals to leave the area or improve the ventilation. It is also possible that events leading to fatal exposure may be more similar to industrial (or home) accidents with toxicity as the cause of death, but with other issues typically associated with industrial accidents also involved (e.g., disregarding safety information, not realizing that neurological effects of these compounds could decrease the ability to escape fatal exposure concentrations due to inability to leave a confined location).

Epidemiological studies represent another tool that could be used to justify the selection of small shops and consumers. However, epidemiology seems to have been underutilized throughout this document. A critical issue is the difference between the occasional or sporadic exposure typical of consumers, the more consistent exposure (though possibly at lower atmospheric concentrations) expected in small shops, and the longer duration but lower level exposures assumed to be associated with larger operations. However, it is not clear from the document if the available epidemiology data suggest occasional use produces acute or persistent health

effects, except in cases in which exposures are very high. This is an important issue because risks due to high exposures could possibly be addressed by measures such as improved safety labeling and educational initiatives, whereas significant risks associated with occasional moderate exposure would suggest the need for a different regulatory response.

A literature review in PubMed on 11-09-2013 using the search terms “methylene chloride” and “toxicity” produced 461 references. A review of these references revealed a number that seemed relevant to this risk assessment that were not cited.

Table 1. Potentially relevant references not cited in the current DCM risk assessment.

- Waddell, W. J. (2003). Comparison of human exposures to selected chemicals with thresholds from NTP carcinogenicity studies in rodents. *Human & Exp. Toxicol.* 22(9), 501-6 (Waddell, 2003).
- Huff, J. (2002). Chemicals studied and evaluated in long-term carcinogenesis bioassays by both the Ramazzini foundation and the National Toxicology Program: In tribute to Cesare Maltoni and David Rall. *Ann. N.Y. Acad. Sci.* 982, 208-30 (Huff, 2002).
- Cooper, G. S., Scott, C. S. and Bale, A. S. (2011). Insights from epidemiology into dichloromethane and cancer risk. *Int. J. Environ. Res. Pub. Health* 8(8), 3380-98, 10.3390/ijerph8083380 (Cooper, *et al.*, 2011)
- Marino, D. J. and Starr, T. B. (2007). Probabilistic dose-response modeling: Case study using dichloromethane PBPK model results. *Reg. Toxicol. Pharmacol.* : RTP 49(3), 285-300, 10.1016/j.yrtph.2007.08.006 (Marino and Starr, 2007).
- Ruder, A. M. (2006). Potential health effects of occupational chlorinated solvent exposure. *Ann. NY Acad. Sci*. 1076: 207-27, 10.1196/annals.1371.050 (Ruder, 2006).
- Slikker, W., Jr., Andersen, M. E., Bogdanffy, M. S., Bus, J. S., Cohen, S. D., Conolly, R. B., David, R. M., Doerrer, N. G., Dorman, D. C., Gaylor, D. W., Hattis, D., Rogers, J. M., Setzer, R. W., Swenberg, J. A. and Wallace, K. (2004). Dose-dependent transitions in mechanisms of toxicity: Case studies.*Toxicol. Appl. Pharmacol*. 201(3), 226-94, 10.1016/j.taap.2004.06.027 (Slikker, *et al.*, 2004).
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Some of these papers were cited and discussed in the 2011 IRIS document on DCM, but others were not, and even those which were cited in the IRIS could have improved the current document by being cited again along with an indication of specific conclusions from the IRIS that were being accepted directly in this risk assessment. However, accepting conclusions directly from previous risk assessment documents opens the process to the possibility of confirmation bias. For example some of the references noted in Table 1, which indicate substantial uncertainty or absence of effects, were not cited in the IRIS (Huff, 2002; Inoue, *et al.*, 2006; Ruder, 2006; Slikker, *et al.*, 2004; Starr, *et al.*, 2006; Waddell, 2003). This may very well

have been due to failure of these references to meet inclusion criteria, but there is no way that this can be determined based on the IRIS 2011 document or the current risk assessment. In addition, there are some very recent references that were published after the 2011 IRIS was written and probably after the current risk assessment was written that are nevertheless quite relevant, such as one from the Upper Midwest Health Study (Ruder, *et al.*, 2013).

The references listed in Table 1 were selected because they were written by well-known scientists in this field, they were published in high quality journals in this field, and/or the title and abstract indicated that they included information that should be relevant to this risk assessment. This is not an exhaustive list, but is only intended to provide several examples. Perhaps the search strategy used by the authors of the risk assessment document and criteria for exclusion or inclusion of references should be described in the document. In addition, there was a somewhat heavy reliance on previous risk assessment documents, which were generally accepted with little or no comment in the current document. Although it is reasonable to make use of previous risk assessments, it should be recognized that there is always a danger that this will lead to a tendency to accept previous results as correct, rather than to take a fresh, critical approach for each new risk assessment. A summary or "history" of key findings and key supporting documents from previous risk assessments that were important in the thinking leading to the current document, might be useful and help confirm that the previous conclusions have not been contradicted by newly published results or that older work was not misinterpreted in previous risk assessments.

A few other specific points in the risk assessment are worth noting with regard to overall quality. For example, the following statement is found in the draft risk assessment document, "Due to DCM's high volatility, the assessment covered exposure scenarios via inhalation and did not address dermal exposures because this route of exposure is not expected to be as significant as compared to inhalation". However, according to one reference, the rate of absorption of DCM through viable human skin is 24 g/m^2h, which is not inconsequential in comparison to the rate of NMP (171 g/m^2h), which is much less volatile than DCM (Ursin, *et al.*, 1995). Another section of the document states, "There is an additional potential concern for immunological effects as suggested by a single acute inhalation study, specifically immunosuppressive effects that may be relevant for infectious diseases spread through inhalation." However, the specific acute study is not identified, no citation is listed, and no further description of these immunological effects is included in the document.

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Ursin, C., Hansen, C. M., Van Dyk, J. W., Jensen, P. O., Christensen, I. J. and Ebbehoej, J. (1995). Permeability of commercial solvents through living human skin. *American Industrial Hygiene Association journal* 56(7), 651-60, 10.1080/15428119591016665.

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