OPPT Trichloroethylene (TCE) Draft Risk Assessment
Final Comments of 9 Member Peer Review Panel
September 5, 2013

Penny Fenner-Crisp (Panel Chair)

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

The draft document fails to articulate satisfactorily that the analysis described within should be characterized as a screening level assessment. Unless one was already familiar with the E-FAST exposure model, one has to dig into the details of the E-FAST model manual to discover that E-FAST V2.0 is described by EPA as a "screening model." "Screening model results are intended to be conservative, meaning that predicted concentrations and exposures are likely to be at the high end of or higher than concentrations that might actually be occurring in a real-world setting. If an exposure estimated by a screening model results in an unacceptably high health risk, then an appropriate next step in the assessment process would be to refine the parameter input or perform the assessment with different and perhaps more complex models. Another response might be to consider monitoring to gather actual emissions data that can be used to estimate exposure" (EPA, 2007, page 1-1). Furthermore, the E-FAST webpage states that E-FAST "provides screening-level estimates of the concentrations of chemicals released to air, surface water, landfills, and from consumer products. …..Estimates provided are potential inhalation, dermal and ingestion dose rates resulting from these releases. Modeled estimates of concentrations and doses are designed to reasonably overestimate exposures, for use in screening level assessment" (EPA, 2013) (http://www.epa.gov/opptintr/exposure/pubs/efast.htm)

Especially since nearly every exposure scenario examined in this document yielded a conclusion of "potential risk of concern," inclusion of some discussion of what a "screening level assessment" is, and what should/could be done in the way of communicating and responding to the results of that assessment becomes very important. A "possible next steps" section also should be included in the Executive Summary, if the document were to be revised.

However, I believe that the Agency acted prematurely in issuing this (screening level) assessment for public comment and in convening a formal scientific expert peer review, given the conclusions reached in it. If all of the conclusions had indicated "no problem, then that assessment should have been peer reviewed externally, to determine if there were outside expert agreement. Presumably, if so, then no further risk assessments would be needed. However, most (and, perhaps, all, if the Agency reverses its decision not to include an assessment of dermal exposure) of the exposure scenarios assessed in the present draft resulted in the conclusion of "indicates potential risks of concern." This begs for refinement of the assessments, on both the exposure and hazard side of the equation. This is essential for any defensible regulatory actions to be undertaken.

Prior to the July 17 meeting, I was inclined to suggest that some revision to the current document would be productive. Revision would be minimal and limited to embellishment with the necessary contextual information I recommended above and in my comments below on Question 1-2.

After listening carefully to the comments and contributions from the other members of the Panel, I have concluded that there would little benefit in revising this draft screening assessment. Rather, I would

suggest that the effort be put into a higher tier, more refined assessment which would include empirical data gathered during the course of real-world uses, e.g., as OPP regularly asks be done for occupational exposures and sometimes for residential exposures, consumer use survey data, evaluation of exposure using additional modeling tools and a revisiting and reanalysis of the choices of toxicity and epidemiologic studies used to describe the health benchmark at the MEC99 level and the rationale for selecting the singular MOE of 30 to apply to the selected studies, each of which have varying degrees of credibility. This current draft screening level assessment could then be attached as an appendix to the new second-generation assessment, and described, in summary form, in the early chapter(s) of the new assessment. I would have saved the resources expended for the current external peer review and spent them on the next-generation assessment.

References

US EPA. 2007. Exposure and fate assessment screening tool (E-FAST). Version 2.0. Documentation manual. US Environmental Protection Agency, Office of Pollution Prevention and Toxics Exposure Assessment Branch. (available at http://www.epa.gov/opptintr/exposure/pubs/efast2man.pdf) (accessed July 10, 2013

US EPA. 2013. Exposure and Fate Assessment Screening Tool Version 2.0 (E-FAST V2.0). (available at http://www.epa.gov/opptintr/exposure/pubs/efast.htm) (accessed July 12, 2013).

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 characterization.

An important question was posed by one of the peer review panelists following the Agency's overview presentation at the July 7 pre-meeting. To paraphrase: "What is the purpose of this document?" To those who are very familiar with Agency legislative mandates and regulatory and communication practices, it may be easy to answer that question. But, for those with only minimal or sporadic contact or interaction with Agency activities and outputs, it may seem a mystery. This document was created to serve as one of several information sources in a complex and potentially lengthy decision-making risk management process. The Agency decided that it was important enough to warrant a review by outside experts. Given that status, it becomes incumbent upon the Agency to include in the document a more substantive discussion of where and how it fits into the decision-making process related to the Existing Chemicals Management Program-including a 'what's next?' module.

The current document was written primarily for "insiders," that is, those Agency risk assessors and risk managers involved in TSCA's Existing Chemicals Program. However, by virtue of the decision to make this assessment available for review and comment, the Agency becomes obligated to write it with "outsiders" in mind as an audience as well—"outsiders" being what EPA describes as the stakeholder community. OPPT's stakeholder community comes to the table with varying degrees of prior knowledge, scientific expertise and sophistication. While not expecting to see a document pitched at an 8th grade-reading level, as are many of the Agency's communications vehicles targeted for the general public, I would expect it to include more context than it currently contains.

Questions on the Exposure Assessment

I have some general comments about the E-FAST model that apply to both Questions 2-1 and 3-1. I am concerned that some of the information used in the model that comes from EPA's Exposure Factors Handbook is out of date or incorrect. The version of E-FAST currently used is dated 2007, and cites

information from the original 1997 version of the Handbook. EPA issued an update of the Exposure Factors Handbook in 2011. Needless to say, I didn't take the time to look for specific mismatches, but I suspect there may be some, some of which will make a difference. One major error that could have been avoided is the age groupings used in the model vs. those recommended in the 2011 Handbook. E-FAST uses groupings presented in the 1997 Handbook. However, these were updated in 2005 (EPA, 2005), before the 2007 version of E-FAST was issued.

E-FAST age groups: Infant (<1), Infant (1-2), Small child (3-5), Child (6-12), Youth (13-19), Adult [Table 3-3, p. 3-74], but less than age 1; ages 1 to 2; ages 3 to 5; ages 6 to 10; ages 11 to 15; ages 16 to 20; and ages 21 to 78 were used in the degreaser and clear protective coating spray use assessments.

2011 Handbook age groups: Birth to <1 month, 1 to <3 months, 3 to <6 months, 6 to <12 months,1 to <2 years,2 to <3 years, 3 to <6 years,6 to <11 years,11 to <16 years,16 to <21 years, >21 years.

Reference

U.S. EPA. (2005) Guidance on selecting age groups for monitoring and assessing childhood exposures to environmental contaminants. Risk Assessment Forum, Washington, DC; EPA/630/P-03/003F. Available online at http://www.epa.gov/raf/publications/pdfs/AGEGROUPS.PDF.

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 the workplace exposure assessment, including estimations for bystander/non-users (e.g., women of childbearing age).

This question brings to mind the old adage attributed to George Box and often quoted: "Models: All are wrong. Some are useful." And, further, a comment made by Dr. John Adgate, currently the Chair of the Department of Environmental & Occupational Health at the Colorado School of Public Health, during a 2002 meeting of the FIFRA Scientific Advisory Panel charged with reviewing one of the several dietary exposure models that the Office of Pesticide Programs employs when conducting its tolerance assessment activities. He said something to the effect that, in his opinion, more than one model should be developed, validated and used for a particular purpose, given our understanding that, at this time, no one model is "the only right one," nor can it precisely characterize the scenario under evaluation.

So I agree wholeheartedly with the exposure experts on the panel that, if the Agency decides to move forward with additional assessments, it should also run the exposure assessments, using different model(s), perhaps, SHEDS-multimedia and some other screening models not developed by EPA, but considered to be credible. Some of these other models were specifically described by these experts (e.g., Dr. Driver mentioned CCEM and he and Dr. Jaycock both mentioned the Nica model.

Just prior to the final meeting of the Peer Review Panel on August 21, the Agency presented a series of Clarifying Questions for the Panel's consideration. One of them was directed to the statements I had made above regarding the use of additional models in the occupational (and, below, the consumer) assessments: "Dr. Fenner-Crisp recommended that the agency consider using an alternate model such as SHEDS for its occupational release and exposure assessment. Please clarify why the SHEDS model is applicable to the agency's occupational release and exposure assessment; why is SHEDS a viable and/or preferred choice for facilities using TCE in degreasing operations compared to the near-field/far-field model that the agency used? Where possible, please provide the supporting reference(s)."

The point I was trying to make when advocating for the use of additional models was that no one model is perfect and fully predictive, and there is great value in employing additional relevant models when conducting an assessment. Yes, one may (will) get different answers, but it does provide an opportunity to better understand the driving factors in an assessment and a clarification of the uncertainties. I was not advocating for a replacing E-FAST, but, rather, using others in addition to. I was not advocating for the use of SHEDS, specifically, but suggesting that an exploration of its components, with or without modifications, and those of other models should be incorporated into any refinement of this initial screening assessment.

During the July 7 pre-meeting, several of the Panel members raised a concern about the decision to exclude dermal exposure from this assessment. I share this concern and recommend that any revised assessment include this route of exposure in it. To support this recommendation, I examined the directions for use for several of the products listed in the Supplemental Product Information document provided to us. For many of the spray formulations, I discovered something like the following on the label:

> "Eye/face Protection: For normal conditions, wear safety glasses. Where there is reasonable probability of liquid contact, wear splash-proof goggles.
>
> Skin Protection: Use protective gloves such as nitrile or neoprene. Also, use full protective clothing if there is prolonged or repeated contact of liquid with skin."

Users, both in the commercial and consumer population, often don't follow the label directions, in fact, never even bother to read them. It's clear to me that dermal exposure will be occurring in the course of use in all of the scenarios being evaluated. Often the object being treated is held in a bare hand. The object may then be wiped dry with a shop cloth, which in turn, with repeated use, gets wet and soaks through to the skin of the holder. Furthermore, there is the question of enforceability of label directions for these products. There are mechanisms to do it for pesticide products, but TSCA doesn't afford that authority and I'm unsure if the other federal agencies involved in worker and consume authority are effective in this matter.

See my comment below about including children ages 11-15 as users in all of the user scenarios. In the commercial scenario, they should be assessed as bystanders as well. In some states, children as young as 10 are allowed to work, although they may be required to get a work permit if they are under 16-18, depending upon state labor law.

Question 3-1: Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models, or information (e.g., information on duration and number of user events) that could be considered by the agency in developing the exposure assumptions and estimates for the hobbyist degreaser and clear protective coating spray uses, and for the bystander/non-users (e.g., children, women of childbearing age).

As mentioned earlier, determine if additional, useful, exposure assessments can be developed using SHEDS-multimedia or other credible non-EPA models.

Use empirical monitoring data, generated in studies conducted either by requirement imposed upon the manufacturers or by EPA alone or in collaboration with other relevant agencies such as NIOSH or CPSC. Ditto for requiring or conducting consumer use surveys.

The two E-FAST model outputs (degreaser and protective coating uses) do not include children in the 11-15 age group as users. I believe that there are many kids in that age group who are "users" under both scenarios; the assessment should include them as well. [For example, both my son and his son and their buddies from their respective generations started rebuilding automobiles, engines included, when they were 14 and my son started working in a gas station repair garage when he was 15].

Question 4-1: Please comment on the strengths and weaknesses of evaluating different endpoints based on exposure durations (i.e., acute versus chronic).

It is perfectly appropriate, and quite commonplace, to match endpoints with durations of exposure, and, then, apply this information to specific subpopulations in addition to, or instead of, the general population.

The body of historical data generally supports the observation that repeated exposures are required to elicit persistent adverse effects in the liver and kidney, although these might occur following less-than-lifetime exposures. As for effects on the immune system, it is clear that long-term effects can be produced following extended exposure. However, I cannot speak for inclusion/exclusion of immune system effects in the assessment of acute exposure, given that there are very few studies on acute exposures and I have little technical expertise with this particular system.

While data are less precise for determining whether or not (and, as importantly, when) a single acute exposure to TCE can lead to developmental effects postnatally, the default health-protective assumption that one dose on any one day of gestation may do so is widely embraced in the risk assessment community. This principle applies when examining the data related to potential cardiac abnormalities in the fetus, but it does not apply to other kinds of observed effects such as fetal weight depression or others that are observed in the presence of maternal toxicity.

Acute effects on the nervous system following acute exposures to TCE have been observed in many studies. Thus, it is appropriate to include an acute exposure scenario in this assessment. But, I believe that neurotoxicity also should be included in the chronic scenario assessment as well. While I did not examine closely the dose-response characteristics for effects observed in specific studies following extended exposure, they have been observed both in humans and animals. Perhaps, their NOAELs/ LOAELs/ BMD_Xs/HECs would be high enough to yield MOEs of no concern. I didn't do that analysis, but simply would note some excerpts from the 2011 IRIS document that support evaluation of extended exposure. These include 1) "Four epidemiologic studies of chronic exposure to TCE observed disruption of auditory function. Further evidence for these effects is provided by numerous laboratory animal studies demonstrating that high-dose subacute and subchronic TCE exposures in rats disrupt the auditory system, leading to permanent functional impairments and histopathology," 2) Overall, the human and laboratory animal data together suggest that TCE exposure can cause impairment of visual function, and some animal studies suggest that some of these effects may be reversible with termination of exposure, " and 3) "Two studies of TCE exposure, one chamber study of acute exposure duration and one occupational study of chronic duration, reported changes in psychomotor responses" (US EPA 2011).

Reference

US EPA . (2011). Toxicological Review of Trichloroethylene (CAS No. 79-01-6). In Support of Summary Information on the Integrated Risk Information System (IRIS) EPA/635/R-09/011F.

Question 4-2: Please comment on the strengths and weaknesses of using multiple values for each type of adverse effect.

One might argue that having and using more than one value for each endpoint is a strength in that it does demonstrate that one can get a variety of results, using different data sets. On the other hand, it doesn't necessarily lessen any uncertainties in the hazard assessment, and it does take more effort and resources. One might be better off selecting a value from the study deemed "best," that is, most representative of the database for each "-icity," based upon an assessment of study integrity/quality, and using just that one in this screening assessment.

Question 4-3: PBPK modeling was employed in the 2011 IRIS assessment for route-to-route extrapolation to develop a corresponding inhalation value from oral studies, some of which involved endpoints not studied or reported in inhalation studies. OPPT supports the approach used in the IRIS assessment. However, OPPT did not use PBPK-derived human-equivalent concentrations from oral studies in the current draft risk assessment, because OPPT focused on a narrow set of TCE consumer uses (e.g., degreasing and arts/crafts uses) that are subject to TSCA and therefore, OPPT's draft risk assessment relied only on inhalation exposure studies that directly mimicked inhalation exposure use scenarios for both adults and developmental life stages. Please comment on whether the 2011 IRIS assessment's PBPK-derived inhalation values from oral studies should be used in the final OPPT risk assessment.

I would hesitate to summarily dismiss all oral studies out of hand from this assessment. To me, the principal criterion for inclusion/exclusion would be the credibility/integrity of the study rather than simply the route of exposure. IF the Agency had conducted a systematic review of the literature and each study as it was developing the IRIS document, it would be a relatively easy task to identify the one best data set to represent the endpoint/duration of exposure/(sub)population to be evaluated. But, there is no documentation to show that this exercise was carried out and I doubt that it occurred.

Therefore, I would recommend that OPPT take another look at the oral studies, make their own determination of their value and include the "good ones" in a refined assessment along with, or instead of, all of the inhalation studies in the current assessment. If OPPT didn't do its own systematic review of those inhalation studies before using them in the screening level assessment, it should do it before keeping them in a refined assessment.

Question 5-1: Please comment on the strengths and weaknesses of the MOE approach used to estimate the chronic, non-cancer risk for the workplace exposures; including non-users.

I've always viewed the MOE approach as the RfD/RfC approach lying on its side. The MOE is a unitless number, derived by determining the ratio of the NOAEL/LOAEL/BMD_X or HEC to the estimated exposure. Embedded in the part-risk assessment/part-risk management determination of the "acceptability" of a specific MOE is a consideration of what uncertainty factors would be appropriate to apply if an RfD or RfC were being calculated for the same example. A strength of the MOE approach is that it is simpler and less time-consuming to calculate and describe than deriving an RfD or RfC because one doesn't have to list and justify each uncertainty factor used. A weakness would be if the application of the MOE approach is not accompanied by a discussion of the rationale/practice/policy by which the judgment of acceptability is made.

In this assessment, it does state what MOE value constitutes the point separating a potential risk concern from one of no concern ("When the hazard value (HEC) is divided by the exposure value, the resulting

number is called the “Margin of Exposure” or MOE. In this risk assessment, if the value is determined as less than 30, there is a potential risk concern; if the value is found as greater than 30, there is no risk concern,” page 11).

Some analysis/justification is offered on page 61 for this choice:

> “ Benchmark MOE values generally range between 10 and 100, depending on the endpoint, the population being evaluated, and a number of other factors generally associated with uncertainty. Generally, each order of magnitude (i.e., factor of 10) is used to represent some uncertainty, such as in extrapolating data from animal studies to humans, from one route of exposure to another, for intraspecies differences within the human population, or extrapolation based on exposure duration of the study (i.e., from short- to longer-term). In this case, all of the PODs were derived using a PBPK model to extrapolate an internal dose in the animal to an internal dose in humans (HEC). In addition, the HECs derived were presented both in terms of median (HEC_{50}) and 99th percentile (HEC_{99}) predictions.
>
> If MOEs are less than the benchmark MOE value, there could be a cause for concern, depending upon the frequency of such exposures and their magnitude. Thus, in this assessment, because the HEC_{99} is more conservative, a benchmark MOE will be 30 (i.e., based on a factor of 10 for intraspecies variability and uncertainty and a factor of 3 for the pharmacodynamic portion of the interspecies extrapolation factor; the latter being reduced based on the kinetic modeling performed to arrive at an HEC.”

The inadequacy of the argument is two-fold: 1) There’s no articulation for what the HEC_{99} is more conservative than, or 2) for why would/wouldn’t an MOE of 30 be satisfactory for a different HEC. In other words, why is this pairing (HEC_{99} and 30) the best choice, in this case?

Question 5-2: Please comment on the strengths and weaknesses of the MOE approach used to estimate the acute risk to consumers; including non-users (e.g., children, women of childbearing age). Specifically, please comment on the decision to limit the analysis to acute exposures without residual concern between events (i.e., once/week for users of the clear protective coating spray, and twice/month for degreaser users).

In my mind, the two sentences in the question are unrelated. I do not see the application of the MOE approach as dependent upon what parameters (exposure duration and (sub)populations) are selected to assess an exposure scenario. As far as the strengths and weaknesses of using the MOE approach for estimating acute risks, they are the same as for estimating chronic, non-cancer risks. [See comments on question 5-1].

As for the second statement, I find it difficult to support the assumptions applied in the two acute scenarios, given that there appear to be no empirical data or even credible surrogate information or consumer survey data available to support them.

Question 5-3: Please comment on the use of a uniform benchmark MOE of 30 rather than a benchmark MOE equal to the composite Uncertainty Factors for each study as identified in the 2011 US EPA IRIS assessment for TCE.

Although more convenient for making comparisons across studies, I do not agree with the use of a uniform benchmark MOE for all studies or endpoints. Each study should be judged on its own merits and deficiencies, and that judgment should be reflected in a study-specific composite uncertainty factor and benchmark MOE.

Another aspect of the exercise as currently implemented is the lack of consideration of the adequacy of the database for characterizing both the qualitative and dose-response elements of each endpoint. I am aware that EPA, in the 2011 IRIS document, stated that there was no need for a database uncertainty factor (other than 1X) to be incorporated into any composite uncertainty factor for studies which contribute overall to the derivation of the RfD or RfC for TCE because the toxicity database, considered in its entirety, was adequate for that purpose. However, in this TCE assessment, adverse endpoints are being evaluated in isolation from one another. Therefore, I recommend that OPPT revisit this issue, asking the question "Is the data set available on Endpoint X adequate for describing this endpoint's qualitative and dose-response elements?" And, if the answer is "No," a database uncertainty factor $\geq$1X should be incorporated into the equation and the benchmark MOE increased to accommodate it.

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

Chapter 3.D. presents a discussion of the key sources of uncertainty and data limitations in the risk assessment. I would generally agree with the arguments made as to which components of the exposure assessment reflect the greatest uncertainty and which ones are lesser contributors. I would differ with some of the statements made regarding the hazard assessment. I would not say that "uncertainty is captured by the use of uncertainty factors." Use of uncertainty factors, particularly default factors, does not necessarily lessen the uncertainties. In fact, it may mask them. Only if chemical-specific factors are employed is the uncertainty reduced. They were not employed in this assessment.

I also do not agree that developing multiple PODs/HECs from different studies for effects on the same system necessarily reduces uncertainty. In this case, it depends on the quality/integrity of each individual study and whether or not each study is evaluating the same set of parameters. This is not the case for TCE.

By selecting the HEC_{99} and very conservative assumptions about exposure, one ends up with a very conservative (that is, health-protective) risk assessment, which assures only the certainty that the potential risk has not been under-estimated. It does little to resolve the uncertainty of the true estimate of risk.

Odds and Ends

1. Clarify that the statement on page 12: " The method EPA used calculated extra cancer risk from benchmarks of concern based on no more than one excess cancer in a population of 100,000 workers (i.e., 1×10^{-5}) …." is actually an OPPT policy, not a universal EPA policy. OPP's target risk for cancer in the occupational setting (i.e., mixers, loaders, applicators) is no more than one excess cancer in population of 10,000 workers (i.e., 1×10^{-4}).

2. Correct the Agency's cancer classification from "probable human carcinogen" to "likely carcinogenic in humans" as per Dr. Melnick's observation.

3. Conduct an internal review of the Forand et al (2012) paper, and incorporate a summary and conclusions in a revise/refined assessment, when conducted.

4. Run SpellCheck

Jeffrey H. Driver

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

The draft document and "characterization" contained therein represents a screening-level assessment and the report should be revised so that the assessment is described accordingly. Screening model (and assessment) results are intended to be conservative, i.e., predicted concentrations and exposures are likely to be at the "high end" of the distribution that might occur in real-world settings. If an exposure estimated by a screening model results in an unacceptably high health risk estimates, then an appropriate next step in the assessment process would be to identify sensitive input parameters and then refine them, and perform the assessment with different and perhaps more complex models. Another response might be to consider monitoring to gather actual product use information (e.g., worker and consumer application methods, amount used, micro-environmental setting, frequency of use, bystander time-activity patterns), emissions data, air monitoring data, etc., that can be used to estimate exposure. This above tiered, step-wise process is an EPA-accepted approach to risk analysis and should be implemented in the case of TCE. The clarity of the hazard characterization, specifically the HEC modeling requires additional discussion and consideration. The uncertainty around the HEC modeling is difficult to understand and is a critical to deciding on the appropriateness of lower bound 99th percentile across the various dose-response relationships considered. I would be informative to also provide a presentation of risks for each toxicological endpoint using traditional MOE derivation (with uncertainty factors documented). Given the early, screening-level nature of the TCE assessment, is not ready for peer review, but rather should be refined by EPA and via stakeholder input. Extending the peer review to colleagues in other EPA offices, such as the Office of Pesticide Programs, could also be helpful, given their experience with workplace and residential settings.

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 characterization.

The draft document should expand presentation of other relevant TCE-related health protection standards and assessments. Workplace and residential environments where TCE products could be used should be further described/characterized. This is critical to realistic modeling of worker and consumer potential inhalation exposures. Existing exposure monitoring data (e.g., indoor air monitoring) should be discussed further. Alternative exposure modeling (e.g., EPA's MCCEM model using probabilistic simulation options) should be considered, particularly of some of the toxicological endpoints should be compared to time-weighted average daily inhalation exposure/dose estimates, rather than near-field, peak exposures. Comparison of model predictions air concentrations and absorbed doses via inhalation to actual monitoring data (e.g., indoor air concentrations), biological monitoring (e.g., blood levels – see NHANES) should be considered. Background documentation should include reference to and summary of these existing data (e.g., indoor air monitoring, biological monitoring).

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 the workplace exposure assessment, including estimations for bystander/non-users (e.g., women of childbearing age).**

1. EPA should refine the risk assessment for workers (and for consumers). While a two-zone, near field model is an appropriate choice for initial modeling and exposure evaluation, the resulting assessment as presented is not appropriate for informing risk management decisions. Areas of refinement for workers for example, include recognizing that OSHA has guidelines in place controls (NESHAP) that functionally limit the upper bound exposures to the current OSHA PEL of 100 ppm (the ACGIH TLV is 25 ppm – EPA 2012 TSCA Workplan Chemical Risk Assessment for TCE). EPA's assessment of workers assumed that the degreasing operations occur during work hours. If the degreasing in fact occurs at the end of the day, there is virtually no exposure; apparently EPA assumed that the degreasing operation occurred in the same room occupied by workers, i.e., the "near field". If, in fact, the degreasing operation occurs in a dedicated room devoid of workers, there is no "near field" exposure. An understanding of the actual work place practices (including ventilation conditions and the use of personal protective equipment) and the proportion of workers experiencing near field exposures is imperative. Distributions for parameters could be used, e.g., ventilation rates) to inform sensitivity evaluation.

2. EPA should refine the screening-level exposure modeling presented and present the full range of exposure factors and risk estimates, e.g., exposure and risk estimates reflecting alternative percentiles for comparisons of exposure distributions to alternative, non-cancer HEC percentiles values. The refined modeling (probabilistic) should include a sensitivity analysis. Further, EPA should justify why an HEC_{99} is being applied to exposure estimates other than acute exposures. Even in the case of acute exposures, if an HEC_{99} is used, the uncertainty factors associated with the PBPK-derived value must be revised. In this context, over the course of 2 weeks to a lifetime, exposures experienced by any given individual will be an average, not an upper bound.

3. The amount of product used for the consumer exposure aerosol application scenario should be informed by actual (or a simulated experiment) product use information. Aerosol products are the most common consumer product form used. A request for relevant data should be issued to the public and the regulated community. Product use studies (e.g., gravimetric measurements before and after use) are often available (or can be developed) to inform this highly sensitive input parameter for indoor air/exposure monitoring. Other sensitive input variables are the micro-environment where the applicator (and bystander) are located, e.g., outdoors or in a garage with an open door, and the associated air exchange range; also, the time spent applying and being co-located with the treated article/surface (currently assumed to be ½ hr, but actual spraying requires seconds). These factors can be addressed by consumer time-activity surveys, or at least can be informed by using ranges or distributions of values consistent with EPA's current exposure factors guidance.

4. The evaporation rate is estimated from equation (3–42 in the E-FAST manual) that provides an estimate of the time for 90% evaporation of a "pure chemical film" based on the vapor pressure and molecular weight. This results in a conservative estimate for consumer products which are mixtures released under non-steady state, intermittent conditions. EPA should also consider comparison of model predictions to any available actual air monitoring for chemicals with comparable uses, methods of application and vapor pressures. Toluene or xylene monitoring following aerosol use might be an excellent surrogate. The model used did not include provision for "sink effects". The lipophilicity of TCE will drive the vapor to adsorb to organics in the room including floor coverings, wall coverings and furniture coverings, and reducing its concentration in air much more rapidly than air exchange alone.

5. The exposure assessment for aerosol application assumes that the same maximum percentage product is used each time, and that no change in formulation occurs over a 57 year duration. It is unlikely the product will exist in 57 years, let alone that it will have the same composition, or that

the individual will use the same product all that time. It also assumes this individual will continue to lacquer-coat objects over their entire adult lifetime. The probability of all of these assumptions co-occurring is extremely low. EPA might be estimating the risk for a single individual in the US.

6. A useful method for evaluating model predictions such as those presented in EPA's TCE assessment is comparison to indoor air monitoring data (e.g., Bakke et al. 2007; Shah and Singh, 1988; Sexton et al., 2005; Santodonato, 1985) during and following an aerosol application relevant to the TCE aerosol products of interest. While these data do not always reflect the same circumstances/scenario as being modeled, they are useful for characterizing potential inhalation exposures to TCE. Thus, while EPA acknowledged reviewing indoor air monitoring data, presenting available TCE and surrogate chemical data can still be useful to "ground truth" model predictions and inform data development recommendations (e.g., chamber studies). When screening-level assessments suggest issues of concern, the cost/risk benefit of collecting additional scientific data (e.g., NIOSH, CPSC) should be considered.

Question 3-1: Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models, or information (e.g., information on duration and number of user events) that could be considered by the agency in developing the exposure assumptions and estimates for the hobbyist degreaser and clear protective coating spray uses, and for the bystander/non-users (e.g., children, women of childbearing age).

Comments to Question 2-1 are relevant to this question. The consumer/hobbyist model should be refined/revised using alternative methods. The Nicas 2 zone model or MCCEM (http://www.epa.gov/opptintr/exposure/pubs/mccem.htm) are options to consider. The Nicas model can accommodate dynamic, non-steady state emission rates and can predict point-in-time and time-weighted average (TWA) exposures for relevant exposure periods. These can be expressed as 24 hr TWA exposures or longer-term, chronic exposures given the number of days per year in which the activity is engaged. Exposures to applicators could also be estimated generically using the EPA's Pesticide Handlers Exposure Database unit exposure values for hand-held aerosol cans. This could provide a conservative estimate of dermal exposure in particular, given that PHED data are largely based on chemicals with lower vapor pressures than TCE. The inhalation exposure estimates based on PHED aerosol spray could be underestimates for this reason.

Question 4-1: **Please comment on the strengths and weaknesses of evaluating different endpoints based on exposure durations (i.e., acute versus chronic).**

1. A systematic evaluation of the quality (including relevance and reliability) of each key toxicology endpoint study is necessary. Further, selection of the appropriate time-averaging period, relevant to each endpoint selected from reliable studies is critically important for deciding what exposure (absorbed dose) metric should be used for risk estimate derivation. Neurotoxicity and developmental toxicity endpoints may, or may not be appropriate for comparison to acute / peak potential inhalation exposure/dose estimates, depending on the time to effect (e.g., trigeminal nerve response, development effects related to exposure on a critical period of gestation versus body weight gain decrease over a period of weeks).

2. HECs derived in the IRIS document from the PBPK model are a daily average computed for continuous exposure (USEPA 2011). However the exposures considered for degreasers and

hobbyists reported in the TSCA work plan is not continuous, but rather is an 8-hour time-weighted average for the worker and a 24-hour average exposure for hobbyist.

3. Just as inhalation toxicity testing results are amortized or adjusted for exposure frequency and duration, so should the exposure of the persons for whom the assessment is being conducted. In other words, toxicity testing results are adjusted from the 4 to 6 hour test animal / subject duration, and 5 to 6 days per week exposure frequency. Likewise the individual's exposure estimates should be amortized over the duration of the toxicity testing, i.e., if an effect was observed on the 13th day of toxicity testing, the consumer exposure should be averaged over 13 days. This was done for "chronic" effects, but not for the "acute" effects. In fact there were no true acute effects utilized in EPA's assessment. The neurotoxicity study duration was 6 weeks, and although neurotoxicity can be observed in humans after a single exposure, it occurs at much higher dosages. Similarly, the developmental toxicity study duration was 13 days, but the some of the effects observed (e.g., decreased fetal weight and increased resorptions) are not consistent with a single dose exposure.

Question 4-2: Please comment on the strengths and weaknesses of using multiple values for each type of adverse effect.

The HEC_{99} are from 2 to 10,000-fold lower than the corresponding POD value. When the difference between the benchmark from an animal study and the HEC_{99} is >100 it suggests that additional uncertainty factors (either within or between species) are not necessary. Moreover, differences of 1000-fold or more call into question the underlying assumptions that produced these hypothetical differences. For example, when endpoints are similar (neurotoxicity or reproductive toxicity) for animals and humans, the ratio of POD to HEC are < 100-fold between species. So what underlying assumptions make the ratio of BMDL to HEC_{99} > 10,000 for kidney effects?

Question 4-3: PBPK modeling was employed in the 2011 IRIS assessment for route-to-route extrapolation to develop a corresponding inhalation value from oral studies, some of which involved endpoints not studied or reported in inhalation studies. OPPT supports the approach used in the IRIS assessment. However, OPPT did not use PBPK-derived human-equivalent concentrations from oral studies in the current draft risk assessment, because OPPT focused on a narrow set of TCE consumer uses (e.g., degreasing and arts/crafts uses) that are subject to TSCA and therefore, OPPT's draft risk assessment relied only on inhalation exposure studies that directly mimicked inhalation exposure use scenarios for both adults and developmental lifestages. Please comment on whether the 2011 IRIS assessment's PBPK-derived inhalation values from oral studies should be used in the final OPPT risk assessment.

Using oral toxicology studies with the same toxicological endpoints would be reasonable provided the oral and inhalation toxicokinetics (metabolites) can be appropriately modeled, and systemic absorbed dose is of interest. Comparison of benchmarks derived from relevant and acceptable oral and inhalation route studies could provide useful weight of evidence insight across animals and human data sources. However, the nature of the study designs and endpoint of interest should be considered, e.g., route-specific / route of entry dose-response. The PBPK model applied in the development of the HECs is apparently not intended to model pregnancy or gestation and as such application of this PBPK model to estimate dose-metrics for developmental effects should be reconsidered / evaluated. Typically the placenta will lower exposure to the fetus by 2 to 10-fold. Since a key concern is developmental toxicity, that should be considered. Comparison of benchmarks derived from oral and inhalation routes can provide useful insight.

Question 5-1: Please comment on the strengths and weaknesses of the MOE approach used to estimate the chronic, non-cancer risk for the workplace exposures; including non- users.

The most significant issue associated with the TCE MOE-based risk assessment approach is the HEC derivation and use of the 99th percentile value. The HEC_{50} values derived by EPA are 1.5 to 1,000-fold lower than the lowest concentration tested in the toxicity tests from which they were derived. Interpolations of magnitudes >10-fold are so far removed from measurements as to be meaningless. When those interpolated dosages are than applied as acute endpoints, it implies that a single dose at these levels of exposure can have an effect. There is no rational scientific support for such estimates when toxicology study durations were a minimum of 13 days. For example, if the HEC_{50} predicted for human kidney effects is correct, there should be clear evidence of adverse effects in human users of TCE at EPA's calculated levels of exposure. Since that effect does not seem to be in evidence, it suggests that both the exposure and HEC_{50} are in question.

Question 5-2: Please comment on the strengths and weaknesses of the MOE approach used to estimate the acute risk to consumers; including non-users (e.g., children, women of childbearing age). Specifically, please comment on the decision to limit the analysis to acute exposures without residual concern between events (i.e., once/week for users of the clear protective coating spray, and twice/month for degreaser users).

See comments regarding Question 5-1. The comparison of acute exposure estimates to repeat dose-based PODs is not appropriate. The specific time domain of "acute exposures" for MOE derivation to the endpoints of interest should be more clearly defined, e.g., 24-hour average inhalation exposures to provide a daily mg/kg/day absorbed dose estimate. Applicators and bystanders time-location patterns are documented in E-FAST supplemental information, however, only acute dose rate (based on peak concentration) and lifetime average daily dose are provided.

Question 5-3: Please comment on the use of a uniform benchmark MOE of 30 rather than a benchmark MOE equal to the composite Uncertainty Factors for each study as identified in the 2011 US EPA IRIS assessment for TCE.

The use of the factor of 30 for the MOE is apparently composed of 10 for intraspecies variability and uncertainty and a factor of 3 for the pharmacodynamic portion of the interspecies extrapolation factor. The factor of 3 may not be appropriate for the HEC 99th percentile. The document should address this issue in the context of different toxicological endpoints (and their underlying studies) of interest.

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

Data limitations and uncertainties are not adequately or transparently described for exposure estimates and associated parameters (e.g., how long, how much and the size of the exposed subpopulations using TCE-containing products within residences) or hazard benchmarks to support risk management decision-making. Also, the toxicological benchmark modeling used requires additional consideration and evaluation (e.g., consideration of oral data; consideration of endpoint relevance to humans; endpoint-by-endpoint risk estimation). The risk estimates for TCE need to be careful considered and informed by additional context/information. For example, consideration of existing TCE exposure and biological

monitoring data (Wu and Schaum 2000). Reducing risks that are unacceptable is the obvious public and environmental health goal, but interpreting the results of the TCE assessment for risk mitigation purposes is premature.

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Montserrat Fuentes

Question 5.2

The margin of exposure (MOE) is the ratio of a toxicologic potency value to an estimated dose or exposure level. The application of the MOE-approach requires reliable animal carcinogenicity data or reliable epidemiological data including very good quality exposure assessment. A concern of using the MOE is that his procedure does not take into account differences that occur in susceptibility between humans and animals nor within animals or humans. The MOE would not determine casual relationships, but associations. For the TCE risk assessment, EPA is using the MOE to estimate non-cancer risk. EPA is using a very conservative value for the hazard, so the risk would not under-estimated. In the MOE, the exposure needs to be carefully characterized (duration of exposure, time in between…).

The use by EPA of the MOE to estimate acute effects could be questionable, due to two important issues. For acute effects, there is less information on the hazard value that is being used, the adopted HEC99 value is obtained using repeated exposure on consecutive days and calculating a 24-hour average. When, in practice, the exposure would likely last just few minutes, with potentially long times in between without exposure allowing for time to recover from the impact of the short time exposure, so using a 24-hour average would potentially overestimate the risk. The other issue is to limit analysis to acute exposures without residual concern between events. In the case of once/week for users of the clear protective coating spray, and twice/month for degreaser users, the risk of residual would be relatively small, so this potentially would be less of a concern.

The overall main issue with the use of the single MOE value is the lack of characterization of the uncertainty in the estimated risk. The fact that the MOE is reduced to the use of two numbers, the hazard value and the exposure value, regardless of how they were obtained, does not provide a quantitative assessment of how much we can rely on that estimated risk. Even if potentially a Bayesian statistical framework is used to obtain the hazard value. As long as just a number is used for the hazard value in the MOE calculations, there is no characterization of uncertainty. This issue could be addressed, by incorporating in the MOE a metric to characterize the uncertainty in the hazard value and/or the exposure value, for instance calculating the MOE with different possible values of both, the hazard and the exposure, under different scenarios to understand the impact in the obtained MOE. An empirical variance of the MOE would explain how variable the MOE would be, and sensitivity analysis would explain how sensitive the MOE is to how the exposure and the hazard are obtained under different scenarios of interest. Comparing the MOE to just a benchmark number, 30 in this case, is questionable, in particular when there is no assessment of the variability and uncertainty in the MOE.

Kathleen Gilbert

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

General comment: In general the characterization represented a reasonably clear and logical presentation of a lot of complex data. However, as raised in the panel discussion, it would be helpful to have a better idea of how this assessment is going to be used. Its purpose and expected readership would help define the style and content of the document.

Specific comments include:

Chapter 1. Scope of Assessment for TCE

This chapter was, for the most part, satisfactory as it provided useful if basic background information on TCE, and most importantly provided the rationales used to decide the focus of the assessment. The rationale for confining the assessment to inhalation exposure and for using multiple endpoints was well-described and logical. The non-cancer endpoints selected, including neurotoxicity and developmental toxicity, made sense based on the human health effects of TCE that have been identified.

On the other hand, the choice of hobbyists as the other population to be included in the assessment was less compelling. The assessment did suggest that this population may face some health risks as a result of their exposure. However, focusing on hobbyists instead of another population at risk from occupational exposure seemed odd. It is true that in the dry cleaning industry use of TCE as a bulk textile cleaner has largely been replaced by PERC or more recently by hydrocarbon or silicone-based cleaners. However, as pointed out in a 2007 document prepared for the California EPA's Department of Toxic Substances Control and the US EPA TCE-containing spot/stain removers (e.g. Picrin, Volatile Dry Spotter, Semi Wet Spotter, ADCO Puro Spot Remover, Caled Fast P-R) are still used as paint, oil and grease spotting agents in the textile cleaning industry.

According to a 2013 book entitled *Chlorinated Solvents. A Forensic Evaluation* published by the Royal Society of Chemistry: "In 2009, TCE was still widely used as a dry-side pre-cleaning or spotting agent and in water repellent agents. TCE is the principle ingredient in Fast PR, 2-1 Formula, Picrin, Puro, SemiWet Spotter, Spra-Dri and Volatile Dry Spotter".

Recent MSDS documents list TCE as the main ingredient for all of these spotters. There are currently in the US about 41,500 dry cleaning facilities employing approximately 4 people/facility (according to IBISWorld). That represents a substantial number of people who could presumably be exposed to TCE on a routine basis. It would be useful for the EPA to clarify why personnel in the dry cleaning industry were omitted from this assessment. Is there information that the TCE-containing spot removers are not widely used or have been discontinued? Alternatively, do the ventilation requirements in dry cleaning facilities make significant TCE exposure unlikely?

Chapter 2. Sources and Environmental Fate of TCE

This is the first time I have been asked to review such a document. So, perhaps there are historical or legal reason to include all of the information in this chapter. The basic physical and chemical properties described in Section A. Physical and Chemical Properties of TCE seemed appropriate, as did the Section C. Production Volume and General Information on Uses. However, from a driving the narrative

perspective the information in Section B. Environmental Fate did not seem to be necessary. Why is the fate of TCE in soil, sediment and groundwater needed for an assessment focused on inhalation of TCE from industrial or consumer products?

Some other clarification would be appreciated. The chapter concludes with:

> "Based on the experimental evidence and environmental fate data available, TCE is expected to have low bioaccumulation potential and moderate persistence."

Everything is relative. Some people consider the human half-life of TCE (around 51 hours) to be long while others consider it short. Is there an official definition of what constitutes "low bioaccumulation" and "moderate persistence"? If not, the use of these terms without qualifiers is less than satisfactory and leaves things up to interpretation.

Chapter 3. Human Health Risk Assessment

There was a good explanation of how TCE is released by small commercial degreasing operations and a comparison of the types of line and batch degreasing machines. The finding that most (66%) of TCE emissions in 2008 were from nonpoint sources (including small industrial/commercial operations) bolstered the choice of personnel at these facilities as assessment targets. However, the discussion regarding difference in fugitive aim emissions of TCE as reported by NEI and TRI was somewhat confusing. Especially unclear was the statement that

> "In light of this, release values from the 2010 TRI will be referenced, but the TCE air emissions will be estimated/adjusted based on the comparison between the 2008 NEI and TRI data (1.7 times the TRI reported value)."

What does "based on the comparison" mean? This should be clarified.

Question 1-2: Please comment on whether appropriate background information is provided and accurately characterized.

- As mentioned there are documents describing the role of TCE-containing spot/stain removers in the dry cleaning industry. These reports suggest that this form of TCE exposure may be worthy of inclusion in this assessment, and have been sent with these comments.

- In Chapter 3 the description of the toxicity endpoints was based largely on the extensive 2011 IRIS Toxicological Review of Trichloroethylene. The authors provided a useful summary of the basic findings and associated data points from selected manuscripts. In describing the TCE hazard database the assessment says:

  > "Based primarily on the IRIS Toxicological Review (US EPA, 2011c), the multiple studies identified for evaluation as points of departure (PODs)[16] for candidate RfCs (*i.e.*, specifically p-cRfCs values derived using PBPK modeling instead of an applied dose/concentration) for non-cancer endpoints are specifically identified below as they are used in evaluating the hazard for this risk assessment."

  However, even in the IRIS document is was not easy to find the criteria used to select particular papers for inclusion. A brief statement explaining selection criteria would be appreciated. Since

many of the metrics used in the assessments were based on a limited number of studies it is important to understand how those studies were selected.

Question 2-1 and 3-1 on Exposure Assessment

- The authors seemed to make logical assumptions about possible exposures based on the limited information available. For example, the rationale for selecting the assessment target population consisting of employees of small commercial shops that perform relatively routine degreasing seemed logical. The assumption that the TCE exposure of the employees of these small shops would be less controlled than employees of a larger facility seems likely. The estimated duration and frequency of the exposure also seemed logical.

- The nonpoint sources were assumed to be batch vapor or batch cold units. Based on the assumptions concerning differences in TRI and NEI emissions the estimate of TCE emissions to air from small commercial decreasing facilities seemed sound, as did the assumption of potential emissions per minute (average release per facility/260 days x 2 hours/day at those facilities) and the estimates of worker exposure taking into account typical and worst-case estimates of room ventilation volumes.

- Their choice of TCE-containing household products based on the NIH Database seemed appropriate. The assumptions used to estimate hobbyist exposure based on duration and number of events seemed reasonable. Estimating exposure for the hobbyists was more problematic. However, it seemed like the E-FAST approach was a logical one.

- The assessment applies the 1.2 decreasing units/facility found at the larger point source facilities based on the Emission Inventory System to estimate the number of smaller degreasing facilities (1,799 nonpoint sources divided by 1.2 machines to equal 1,483 small industrial facilities. It is not intuitive why the number of machines found at a large facility (which logically might be expected to have more than one machine) can be translated to small nonpoint sources (which logically might be expected to have only one machine/facility). Clarification on this point would be appreciated.

Question 4-1: Please comment on the strengths and weakness of evaluating different endpoints based on exposure durations.

- It is clear that the impact of TCE on different systems varies according to the duration of exposure. Neurotoxicity can be induced after a brief exposure, while immunotoxicity usually requires chronic exposure. Therefore, although it may be more complicated than evaluating a single cadre of endpoints, a comprehensible and precise hazard assessment requires evaluating different endpoints based on exposure duration.

- Bioaccumulation of TCE, described as low, was dismissed from the exposure calculations. The following text described TCE half-life:

  > "Half-lives are useful indicators for bioaccumulation potential. Assuming first-order kinetics, >90 percent is eliminated after four half-lives and about 99 percent after seven half-lives (Shen, 2008). Thus, assuming a half-life of about 51 hours (*e.g.*, the longest value listed in Table 3-15), TCE would be mostly cleared by approximately

200 hours (*i.e.*, about eight days) with nearly complete clearance by approximately 350 hours (*i.e.*, a little over two weeks)."

While TCE bioaccumulation is definitely low compared to certain toxicants such as mercury, it is not clear from the half-life description that it can be completely dismissed, especially in the case of the personnel in the small degreasing facilities whose estimated exposure frequency is 260 days per year for 2 hours per day.

Question 4-2: Please comment on the strengths and weakness of using multiple values for each type of adverse effect.

The OPPT seems to have done a good job deriving PODs and HEC_{99} from the existing data. Human data sets are often insufficient for quantitative risk assessment so the inclusion of animal studies was crucial. It is only to be expected that these will vary according to the target organ system. As described in the assessment there is an approximate 1000-fold difference between the lowest and highest lower-end HEC_{99} based on the organ system. Using all six endpoints provides the more comprehensive and precise risk assessment. However, a better justification of using HEC_{99} as opposed to another benchmark would be helpful.

Question 4-3: Please comment on whether the 2011 IRIS assessment's PBPK-derived inhalation values from oral studies should be used in the final OPPT risk assessment.

This question can be argued from both points of view. Since the assessment is focused on inhalation exposure it makes sense to derive their risk assessment from the data of inhalation studies. On the other hand, including data extrapolated from oral exposure studies would provide a richer data base and presumably increase the confidence of the metrics. The only caveat would be that in some cases, such as certain immunotoxicity endpoints (e.g. lung inflammation) oral and inhalation exposure would be expected to yield different results. In those cases, inhalation only exposure studies seem more appropriate.

Questions 5: Please comment on the strengths and weakness of the MOE approach, and whether the document has adequately described the uncertainties and data limitations in the methodology used.

- Depending on the approach used to determine the POD and to estimate exposure it is possible to derive very different values for the MOE. However, it can be a very useful risk assessment tool if the endpoint is carefully selected and the derivation of the values carefully justified. Especially important is the shape of the dose-response curve at human relevant doses. This information in the current setting requires a lot of assumptions, especially for the non-users. However, it seems like the best approach to use even with the limited quantitative data available. THE OPPT has fairly described the uncertainties regarding consumer TCE exposure.

- Since benchmark MOE values usually range from 10 and 100, the selection of 30 as the benchmark for the TCE assessment seemed logical, especially in view of the factors used to account for intraspecies variability and the pharmacodynamic portion of the interspecies extrapolation factor. However, it would be helpful to include a better discussion of the uncertainty factors that were used (or omitted) to derive the particular benchmark.

- The OPPT described the uncertainties with both “typical” and “worst-case” scenarios. They pointed out the greatest uncertainties in the hobbyist groups and consumer use in general. This was useful, but as pointed out above, could have been more in-depth.

Public comments

I thought some of the public comments raised interesting points. I would appreciate clarification on these specific comments:

- The point was made that TCE is already adequately regulated under the Clean Air Act. Does that pertain to the exposure scenarios described in the assessment?

- It was stated that the assessment was based on exposure data that predated regulations on vapor degreasing. Is that true, and if so, would it expect to alter the risk assessment?

Some other comments seemed more disingenuous and self-serving. Complaints that the EPA used worst-case rather than more likely estimates of exposure and risk seemed unwarranted, as did the suggestion that possible TCE substitutes used as a result of the assessment could turn out to be more harmful for the environment. The view that the assessment needed to use measured rather than modeled data of exposure was impractical.

General comment

The assessment represented a good attempt to devise reasonable risk assessment predictions based on a large, if somewhat disparate, body of literature. In an ideal world this assessment would be based on measurements of internal TCE levels following different types of human inhalation exposure scenarios. It would also include more definitive epidemiological data of human health responses to these scenarios. However, in many cases this data is not available, and unlikely to become available, at least in the foreseeable future. This means that exposure modeling and data extrapolation is required for risk assessment. This seems appropriate. Having said that, additional data including descriptions of TCE air levels following experimental releases, a better justification for the studies used to derive the metrics, possible sensitivity analyses, and more detail about the uncertainty factors used to determine the benchmarks would bolster the assessment. Yes, the assessment document can and should be improved. However, in my opinion, this important risk assessment should not be sidelined by the need to reach a complete consensus by all interested parties.

Supplementary comments in response to EPA clarifying questions presented at August 21, 2013, TCE post-meeting

See ‘TCE_Gilbert Supplemental Material.pdf’ for:

1. Spotting Chemical Fact Sheet;
2. DTSC Spotting Chemical for Web;
3. Material Safety Data Sheet: Fast – PR; and
4. Material Safety Data Sheet: Picrin.

Mike Jayjock

General Comment:

It is my opinion that uncertainty ultimately determines whether an assessment is considered to be definitive and ready to be used for regulatory control decisions or a screening level evaluation begging for and identifying more certain data to render a definitive evaluation.

One never has complete information and this requires those doing the assessment at every level to trade conservatism for the missing and more confident knowledge. This need drives up the uncertainty and ultimately determines the utility of the effort.

The exposure assessment in this document is primarily driven by airborne concentration modeling and the models are in turn driven by their primary predictor variables; namely, emission rates and fresh air ventilation rates. For the most part, these are first principle models and given good inputs will render reasonably accurate predictions of exposure. Some of the primary model inputs used in the current assessment and in suggested modeling approaches would benefit greatly from relatively little additional work and this work should be considered.

A high level of uncertainty in both the estimation of exposure and hazard can be tolerated if the prediction of overexposure vis-à-vis an MOE approach is high enough that even considering the uncertainty bands around exposure and hazard the putative risk is clearly significant and in need of regulation. Thus even a highly uncertain risk assessment could be considered definitive given this condition.

My read of the uncertainty in the exposure assessment portion of this assessment is that it is significant but that it can be narrowed with relatively little effort. My sense is that the exposure assessment of TCE can be improved especially in the realm of consumer exposure via the use of better models, better experimental estimates of the emission potential and a better understanding of the size of the exposed populations; however, whether this effort is worth this effort and expense ultimately depends on the overall uncertainty analysis and the distance between bounded predicted exposure and bounded predicted hazard potential. If these error bands significantly overlap then my sense is that this is a screening assessment in need of further refinement. If not, it should be considered complete enough for regulatory action assuming the exposed subpopulations are large enough to be of concern.

I have a much better feel for the relative potential error bands around the assessment of TCE exposure in the various scenarios under consideration than I do for the hazard assessment. Indeed, what I did not get from this assessment is a reasonable sense or understanding of the uncertainty around the hazard assessment. Before the meeting with my colleagues, I thought that this likely is as much a result of my lack of understanding of these complex measures and descriptions as it is of the presentation within the report. I thought that the complexity of the approach is simply too high to allow for a presentation of the uncertainty around hazard that I, or technologists with a similar background, would understand.

During the meeting I heard comments from colleagues with strong backgrounds in hazard assessment express essentially the same opinion relative to the hazard assessment. That is, that did not think that such high putative hazard as was ascribed to TCE in this report is reasonable or, at the least, it was not reasonably supported within the document. For me this translates into a very large error band around the ascribed hazard level used in the report; namely, the lowest HEC_{99} values.

Clearly, more work is needed on both the exposure and hazard side of this evaluation to tighten up the exposure assessment and to provide further justification or explanation of the exceedingly low HEC_{99} values used in the MOE analysis.

Question 1-1: Please comment on whether the characterization provides a clear and logical summary of EPA's analysis. Please provide specific suggestions for improving the document. [Lead Discussant: Gilbert]

I found the report to be generally well organized even though it is obviously very complicated and challenging to understand. In a summary document one always has to balance the need for sensible brevity with the requirement that there is enough information provided that it is understandable. My expertise is in exposure assessment and I generally found these aspects of the report to be quite clear and logical with two notable exceptions covered herein.

Appendix D cites Keil *et al.* (2009) as the source of information for the 2 zone model outlined in this section. The only Keil *et al.* (2009) reference in the document is a toxicology study:

> Keil, D. E., Peden-Adams, M. M., Wallace, S., Ruiz, P., and Gilkeson, G. S. (2009). Assessment of trichloroethylene (TCE) exposure in murine strains genetically-prone and non-prone to develop autoimmune disease. *J. Environ. Sci. Health A Tox Hazard Subst Environ. Eng* 44(5), 443-453. (as cited in US EPA, 2011c).

This is not the Keil, et al. (2009) publication that outlines the Nicas 2 zone model. That reference is available from the American Industrial Hygiene Press[i]:

It is clear to see where the confusion came from with two Keil *et al* 2009 references; however, the second one should be included in the assessment and distinguished from the first.

Another area of confusion for the reader in Appendix D is the missing notation in the following paragraph cut and pasted from the report:

> "For the purposes of mass transfer from and to the near-field, the free surface area, is defined to be the surface area that is available for mass transfer; the … will not necessarily be equal to the surface area of the near-field. For instance, if the near-field is defined to be a rectangular region, as illustrated in Figure D-1, the near-field floor will not be available for mass transfer; thus, the … will be less than the actual surface area of the near-field:"

Of course *FSA* should be inserted in the blanks but it does give the reader pause and someone not familiar with the model even more pause.

As stated above and repeated through this review, my expertise is primarily in exposure assessment; however, in order to do risk assessment I have, of course, had to become reasonably knowledgeable in the realm of hazard assessment and toxicology. I found the presentation of this aspect to be particularly difficult to follow requiring considerable review of the referenced materials in order to make any reasonable sense of the approach. For example we are told in the assessment:

> "In this risk assessment, all of the hazard values were derived using a ***special mathematical model*** as determined by US EPA (2011c). The modeling exercise used test data from both animals and humans to derive values called Human Equivalent

> Concentrations (HEC). Although many HEC values were calculated by the IRIS program, in this assessment a more conservative value was used (i.e., the lower bound 99th percentile HEC value) for each of the non-cancer adverse effect outcomes evaluated." [Emphasis added.]

From my perspective as a reader attempting to understand what was done, more explanation should have been provided regarding the specifics of the modeling and the HECs. I will have more to say about this aspect in my later comments.

Finally, the explicit estimation of the size of the population(s) at risk in the various exposure categories/scenarios and the uncertainty around these estimates should be included within the 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 characterization. [Lead Discussant: Ryan]

The assessment appears to me to be reasonably well documented in the realm of exposure assessment for the models being considered with one notable exception, indoor air monitoring. The report mentions that indoor air concentrations of TCE are expected to be higher than ambient levels (which are summarized in the document). It also acknowledges the existence of indoor air studies that included TCE but it does not summarize them. Even though these studies did not focus on the exposure from the use of TCE in consumer products, their summary could provide valuable information on the levels extant in indoor air and give some insight or clues as to the magnitude of chronic exposure potential and the size of the subpopulation for this exposure within residences.

As discussed below there are additional exposure models that should have been considered and used in the assessment. I will outline these in detail later in my responses.

I am not qualified to comment on the completeness of the available toxicological studies of TCE but my colleagues on the panel cover this area in their comments. Given my experience, however, it does appear to be a significant amount of information, covering many important end points.

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 the workplace exposure assessment, including estimations for bystander/non-users (e.g., women of childbearing age). [Lead Discussant: Driver]

The first subject I wish to discuss is the dermal exposure potential from this compound. Given the volatility of the TCE, I understand the Agency's tendency to dismiss dermal out hand. Indeed, for every risk assessment I have seen or done over the years on compounds with a relatively high vapor pressure, the risk has been dominated by inhalation exposure.

Clearly there will be some dermal exposure to TCE especially during the industrial and consumer use of degreasers and other consumer products. Thus, it is understandable that not doing an explicit quantitative dermal exposure/risk assessment has been an area for criticism. Having said this, my sense is that a reasonable worst case dermal scenario should be outlined and conducted to demonstrate that the dermal route is minor in this case and by analogy for all other scenarios under consideration. Useful models for dermal exposure assessment include the dermal modules in Consexpo 4.1[ii] or the IH Perm model offered

by the AIHA (reference vi). The option in E-FAST2 to estimate absorbed dose from dermal exposure can also be used given a permeability coefficient for TCE which should be available from the literature.

I found the inhalation model choice, model inputs and treatment of the industrial inhalation scenario to be well done with the possible exception of the "typical ventilation" rate. The pieces of this scenario and model that appear to be adequately supported based on my experience:

- The critical parameter of evaporation emission rate of 16.7 grams/min is well documented from different sources.
- Using a default factor of 90% for capture efficiency of local exhaust ventilation (LEV).
- The size of the model near field volume leading to potential breathing zone concentration for the workers around the degreaser.
- The use of the steady-state 2 zone model for an industrial facility that is running continuously.
- The use of a random air flow rate of 10 cm/sec from the Maynard study.

The only questionable variable in my opinion is the use of 3000 cfm as the "typical value" for general ventilation in an industrial room. Consider an industrial room 20' x 20' x 20' or 8000 ft^3 ventilated at 180,000 ft^3/hour (3000 cfm) is equivalent to over 20 air changes per hour. A room twice this volume would have 10 air changes per hour at this rate. Hot industries, clean rooms, laboratories or industrial space with a lot of LEV can get to these levels or higher; however, my experience has been that industrial rooms without special exhaust will be ventilated in a range of 2-5 air changes per hour. I would expect degreasing operations without local exhaust to be in this range. Perhaps reviewing some of the previous work in these facilities would reveal this level of ventilation. In any event, 3000 cfm may not be "typical" case but more likely the best case for general ventilation.

Lowering the presummed general ventilation rate in industrial rooms will increase the predicted exposure for bystanders but will do little for the predicted exposure to workers in the near field which is dominated by the inter-zonal ventilation.

An important area of uncertainty relative to this exposure assessment occurs in the determination of the actual subpopulation of workers who might be exposed to the model-predicted values. Of course, the actual exposure to TCE of this population will be a function of the amount of time they spend in the near field and far field within the degreaser room and their actual use of person protective equipment.

Question 3-1: Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models, or information (e.g., information on duration and number of user events) that could be considered by the agency in developing the exposure assumptions and estimates for the hobbyist degreaser and clear protective coating spray uses, and for the bystander/non-users (e.g., children, women of childbearing age). [Lead Discussant: Jayjock]

I believe that E-Fast2 CEM is not the appropriate model to use for the primary person exposed in these scenarios. It could be useful for residential bystander exposure estimation, however.

The E-Fast2 CEM inhalation exposure model is based on a dual zone model with the entire room where the source is located acting as the primary zone for predicting user exposure and the rest of the house as the remaining zone. Both zones are considered to be well mixed —as such, this model does not estimate

exposures that are near to the user (near field). Instead it estimates the average concentration within the room which is always significantly (sometimes dramatically) lower than the breathing zone concentration of someone performing a VOC spraying operation literately at arm's length.

The Nicas 2 zone model was specifically designed for these types of exposures. In its dynamic form, it can predict point-in-time and time-weighted average (TWA) exposures for operations of any length. These can then be readily converted into 24 hr TWA exposure or chronic exposures given the number of days per year in which the activity is engaged. A suggested near field volume would be a hemisphere 1.5 meter in diameter which would include the source and the breathing zone of the person doing the spraying on a flat horizontal surface.

For average random air velocity used by this model, a National Academy of Science publication[iii] lists average residential indoor air speeds as occurring in the range of 0.05 to 0.3 m/s (3 to 18 m/min). Assuming that this range is log-normally distributed with the majority of values on the low end of the distribution, 0.07-0.1 m/sec would appear to be a reasonable estimated range. This range is also in line with some very limited field testing of residential volumes done by this reviewer.

The evaporation rate of the TCE could be estimated by taking the amount used per session, assuming complete evaporation of the TCE during the session and thus dividing this mass by the time of the activity to render an average emission rate. Another approach would be to determine a first-order decreasing emission rate using the relationships outlined in the E-FAST2 documentation copied below:

In the case of a general purpose cleaner, the equation for exponentially declining emissions for each instantaneously applied segment is as follows:

$$E(t) = E(0) \times \exp(-kt) \qquad \text{(Eq. 3-41)}$$

where E (t) is the emission rate (mass/time) at time t (in hours), E (0) is the initial emission rate at time 0, k is a first-order rate constant for the emissions decline (inverse hours), and t is elapsed time (hours). The value of k is determined from an empirical relationship, developed by Chinn (1981), between the time (in hours) required for 90 percent of a pure chemical film to evaporate (EvapTime) and the chemical's molecular weight and vapor pressure:

$$EvapTime = \frac{145}{(MW \times VP)^{0.9546}} \qquad \text{(Eq. 3-42)}$$

The value of k is determined from the 90 percent evaporation time as follows:

$$k = \frac{\ln(10)}{EvapTime} \qquad \text{(Eq. 3-43)}$$

An alternative manner of determining k is a relatively simple experimental approach presented by Keil and Nicas.[iv]

Both of these methods (the E-FAST documentation shown above and the Keil/Nicas method) assume a bolus of TCE at time equal zero. In reality the TCE could, and mostly likely would, be applied over the entire time of use. The E-FAST2 documentation presents a more detailed algorithm which considers this situation by combining constant application and exponentially declining emissions:

E (0) can be determined from the fact that the integral of Equation 3-41, which accounts for all chemical mass released (i.e., applied mass times chemical weight fraction), is equal to E (0)/k. However, the equation for the time-varying emission rate resulting from the combination of constant application and exponentially declining emissions (Evans, 1994) requires knowledge of only the total mass released and k.

$$ER(t) = \frac{M}{ta}\left[(1 - e^{-kt}) - (1 - e^{-k(t-ta)}) \times H_{(t-ta)}\right] \qquad \text{(Eq. 3-44)}$$

where:

ER(t)	=	Emission rate at time t (mg/hr)
M	=	Chemical mass to be emitted (mg)
ta	=	Application time (hr)
k	=	First-order rate constant for emissions decline (1/hr); see Eq. 3-43
t	=	Time (hr)
$H_{(t-ta)}$	=	0 if t-ta < 0
	=	1 if t-ta > 0

It is suggested that all three modeling methods be used; namely, an assumed constant emission rate, a first-order decreasing emission rate after a bolus release and an emission rate combining constant application and exponentially declining emissions. The results of these three modeling approaches should be analyzed and compared.

Unfortunately, this reviewer is not aware of any software modeling code that includes this algorithmic description of time varying emission rate and the Nicas 2 zone model or the eddy diffusivity model discussed below. This can be readily done by programmers, however.

Another general model specifically designed for estimating the inhalation exposure potential from small sources near to the user is the Eddy Diffusivity model. This model provides a gradient of concentration/exposure from a point emission source for any point-in-space. It can predict point-in-time and integrated TWA concentrations for the point-in-space that would represent the nose/mouth of the user.

One of the challenges previously with this model was the required input of the eddy diffusivity coefficient (D). These values have been historically difficult to measure and very few were available. This issue has been recently addressed by experimental work reported out of Stanford University[v] in which it is now possible to estimate D from information on the ventilation rate within the residence and the dimensions of the room in which the activity is occurring.

It is further suggested that E-Fast2 be used for by-stander exposure in residences as it is currently done in the report.

The complete form (point-in-time and time-weighted average concentration) Nicas 2 zone and eddy diffusivity models are provided in a thoroughly reviewed and vetted freeware spreadsheet (IH MOD) available from American Industrial Hygiene Association (AIHA)[vi]. Available models include assumed constant sources or bolus sources (e.g., spills) declining via first order kinetics. All of these models are thoroughly documented in a companion publication by the AIHA (reference i). As mentioned above IH MOD does not handle the input of combining constant application and exponentially declining emissions and this would have to be subsequently coded, possibly in the next revision of IH MOD.

Please note that much of the uncertainty in this modeling is related to specifically how much product is sprayed during the degreasing (or coating) operations and exactly how much TCE is in the product. Simple experiments simulating the products' use while measuring the weight loss of the containers will provide the analysis with very confident data on this important variable. Gas Chromatographic analysis of

the products would settle the issue of percentage TCE. It appears to this reviewer that these data represent a significant amount of confident knowledge for a relatively small investment.

Finally, any modeling analysis would benefit from the application of a sensitivity analysis to determine which variable are driving the estimations of exposure. This would in turn inform which type of future work would provide the biggest returns on the reduction of uncertainty.

Question 4-1: Please comment on the strengths and weaknesses of evaluating different endpoints based on exposure durations (i.e., acute versus chronic). [Lead Discussant: Driver]

Looking at different endpoints is strength in that one gains a clearer perspective on which organ systems are affected and which one(s) might comprise the critical health hazard from exposure to TCE. If one accepts that more information is better than less, this approach has no weakness.

Studies of chronic endpoints are appropriated identified and used in comparison with occupational exposure which can occur daily for a working lifetime. This is strength of this analysis.

To the extent that acute end-points are appropriately determined in toxicological tests their comparison to the acute exposures extant in the human consumer exposure to TCE is a strength; however, this situation does not appear to be at work in this analysis.

In the area of consumer exposure it is an acute event lasting perhaps tens of minutes or a few hours at most. Thus for members of the general public using these products there is a bolus of exposure in a relatively short time frame and any testing and understanding of the physiological risk associated with this brief and relatively intense exposure is appropriate. This is especially true for adverse endpoint events that are “timing critical” such as the acute or daily exposure on the most susceptible day of gestation.

To the extent that the risk of adverse response as it relates to dose rate is known then the estimation short (or long) term exposures matched to a toxicological benchmark applicable over the same time interval has obvious value. To the extent that the effect of dose rate for acute exposure is either unknown or very uncertain, this approach has limited utility. This subject will be discussed in more detail below but suffice it to say that essentially all of the “acute” hazard studies come from dosing the subjects repeatedly over a number of days and may not provide a good hazard benchmark for comparison to exposures that happen during a single day and are not repeated for a long time.

Question 4-2: Please comment on the strengths and weaknesses of using multiple values for each type of adverse effect. [Lead Discussant: Portier]

From my reading of the document I note a few reports of multiple values for each type of adverse effect but I also do see a range of adverse effects reported within different target organs. For example, within neurotoxicity the following studies/adverse effects are noted and reviewed: Trigeminal nerve effects in humans, Changes in wakefulness in rats and Decreased regeneration of sciatic nerve in mice. Clearly the advantage of doing both is to show the width and depth of available data and the range of responses leading to different HEC_{50} and HEC_{99} values. This reported range also helps to feed the evaluation of the uncertainty associated with these effects and the predicted effect values for humans.

Question 4-3: PBPK modeling was employed in the 2011 IRIS assessment for route-to-route extrapolation to develop a corresponding inhalation value from oral studies, some of which

involved endpoints not studied or reported in inhalation studies. OPPT supports the approach used in the IRIS assessment. However, OPPT did not use PBPK-derived human-equivalent concentrations from oral studies in the current draft risk assessment, because OPPT focused on a narrow set of TCE consumer uses (e.g., degreasing and arts/crafts uses) that are subject to TSCA and therefore, OPPT's draft risk assessment relied only on inhalation exposure studies that directly mimicked inhalation exposure use scenarios for both adults and developmental lifestages. Please comment on whether the 2011 IRIS assessment's PBPK-derived inhalation values from oral studies should be used in the final OPPT risk assessment. [Lead Discussant: Willhite]

This is clearly not in my area of expertise; however, it strikes me that if there are sufficient inhalation studies to render a competent analysis then the approach used by the OPPT seems reasonable and appropriate to me. The obvious strength is that the inhalation studies use the same route of exposure as the dominant route predicted for human exposure. If the oral studies provide much more and better data and there is a high degree of confidence in their quality then it would seem that they should be used.

In examining the report, I found two comparisons of oral versus inhalation studies that stand out. It is reported in Table F-1 and shows very small HEC_{99} values for decreased thymus weight and increased anti-dsDNA in the mouse. Presumably these are important effects that were either not noted or not looked for in the reported inhalation studies of the mouse. The same situation is true of the very low HEC_{99} reported for heart malformations in oral developmental studies in female rats dosed throughout gestation. The difference is striking and should be addressed and seems to argue for using the oral data.

Question 5-1: Please comment on the strengths and weaknesses of the MOE approach used to estimate the chronic, non-cancer risk for the workplace exposures; including non- users. [Lead Discussant: Jayjock]

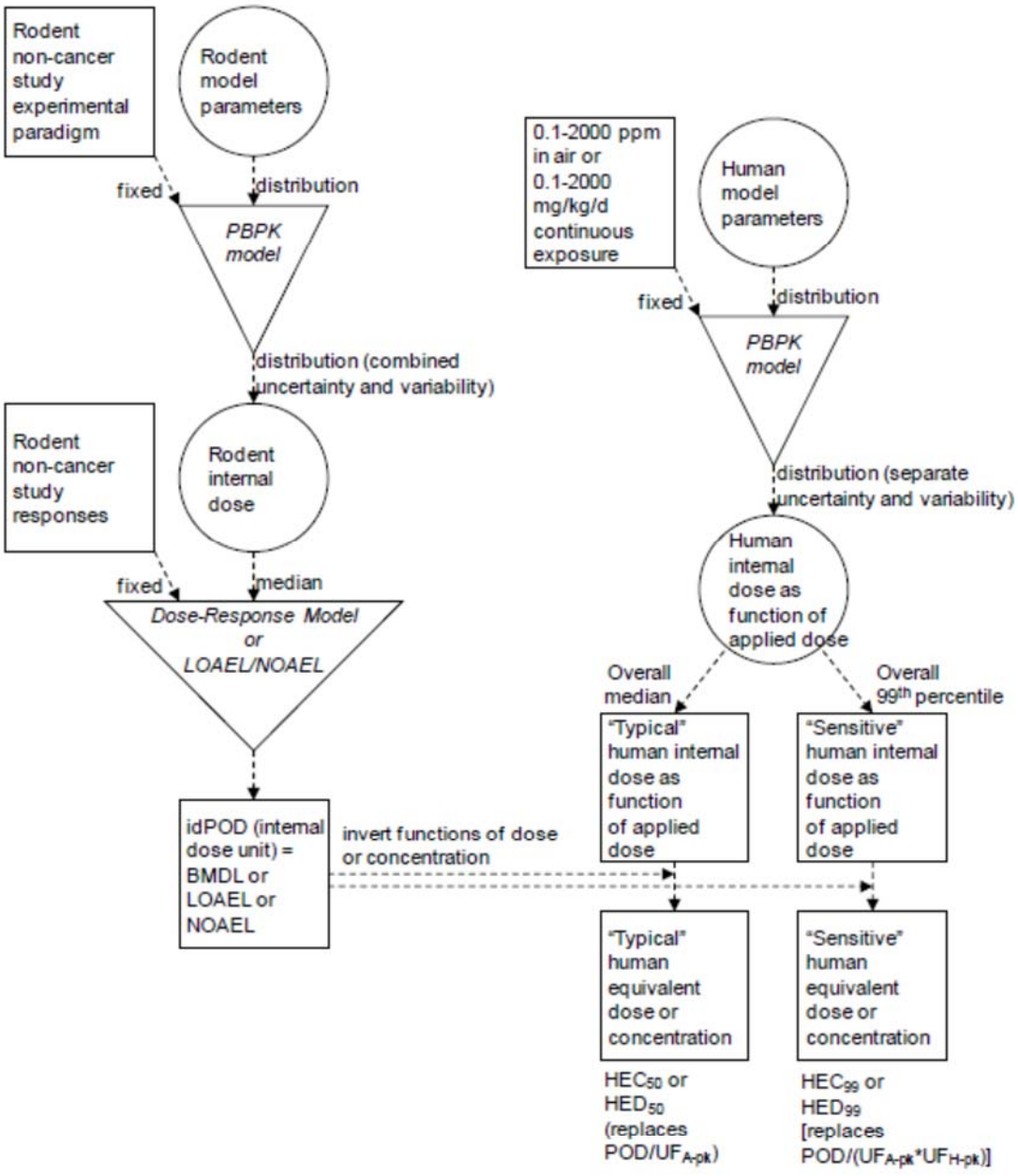
From my perspective the largest strength of the MOE approach lies in its apparent simplicity. That is, it is a simple unitless ratio of exposure to hazard with large MOE values providing some confidence of relative lack of risk and small number indicating significant risk. The other strength is that we are dealing with potentially true chronic exposure in that workers can typically receive a daily exposure every day for many years and thus comparisons of this chronic exposure to output of extended repeat dose toxicological studies makes sense.

The predominant weakness of this MOE approach, in my opinion, lies in the complexity of the hazard benchmark, namely, the HEC_{99}. This complexity presents a challenge to just about anyone who is not a PBPK modeler/toxicologist in trying to understand it. It is my understanding that the MOE approach in this assessment is a ratio of the estimated exposure and the hazard expressed as the HEC_{99}. The HEC_{99} is the lower-end of the range of hazard values for the "sensitive" human (the 99th percentile, or HEC_{99}) for each target organ/endpoint. The flow-chart copied below from the EPA 2011 Toxicological review of trichloroethylene[vii] provides what I found to be the best explanation of this important value; however, any benchmark requiring a 15 component flow chart in 2 streams is clearly quite complex.

There is a significant amount of uncertainty in this treatment when one compares the HEC_{99} values for ostensively the same effect in different species and large differences emerge as a result of this comparison. For example, comparison of sperm effects in human males (mean years on the job = 5.1 years) indicates an HEC_{99} of 0.5 ppm while a study in male mice exposed 6 weeks at 1,000 ppm has an HEC_{99} that is 134 fold higher at 67 ppm. Indeed, an average of 5.1 years of exposure is more chronic than 6 weeks which may have accounted for at least some of the difference.

An advantage of this HEC_{99} approach is that one can gain a quantitative appreciation for the more sensitive non-cancer end-points. Adverse effects to the kidney really stand out showing very low HEC_{99} values and subsequently low MOEs.

The biggest disadvantage for me is that the HEC_{99} this is a deterministic number. It is provided as a value in the tail of a distribution but the elements of any epistemological uncertainty feeding this distribution and value have not been made obvious. Indeed, because of my lack of knowledge about the details of the PBPK modeling and these uncertainties, I have little sense for the error bands around it relative to what might be the "actual" HEC_{99}. During our meeting, most my colleagues who have a much better understanding of these hazard assessment techniques voiced serious concerns about the level of uncertainty extant in the HEC_{99} values driving the characterization of risk in this assessment.



Square nodes indicate point values, circle nodes indicate distributions, and the inverted triangle indicates a (deterministic) functional relationship.

Figure 5-2. Flow-chart for dose-response analyses of rodent noncancer effects using PBPK model-based dose-metrics.

Question 5-2: Please comment on the strengths and weaknesses of the MOE approach used to estimate the acute risk to consumers; including non-users (e.g., children, women of childbearing age). Specifically, please comment on the decision to limit the analysis to acute exposures without residual concern between events (i.e., once/week for users of the clear protective coating spray, and twice/month for degreaser users). [Lead Discussant: Fuentes]

Essentially of the same strengths and weaknesses I outlined in Q 5-1 are operational here with one notable exception; namely, the use of repeat dose toxicity data in an MOE along with acute exposure data represent a significant weakness in the approach. In this instance we are dealing with acute exposures lasting tens of minutes or, at most, hours and calculating a 24 hour average exposure for that one day of exposure. This exposure in the real world is followed by long periods of time with no exposure. During these periods of no exposure there is almost certainly effective elimination/detoxification of the TCE and the opportunity to repair any physiological damage done from that brief exposure.

As best as I can tell, there is only one set of HEC_{99} values and these were developed from repeat dose studies in which the subjects were exposed on consecutive days. My sense is that this comparison of one day acute exposure with many day chronic (or repeat dose) hazard benchmarks is very conservative perhaps to the point of being not valid. I understand that the toxicology data do not exist for the most part to support it but technically what is needed is an acute HEC_{99} developed from single day acute dosing protocols.

At the least, this inherent weakness should be highlighted in the assessment and the conservative nature of this comparison noted.

Relative to the decision to limit the analysis to acute exposures without residual concern between events (i.e., once/week for users of the clear protective coating spray, and twice/month for degreaser users), my advice is that that the daily exposure should be put into an annual (chronic) average exposure and compared to the chronic hazard benchmark. It is a relatively simple and straightforward task that is anticipated to show a relatively high MOE for consumer chronic exposure and risk to TCE.

Question 5-3: Please comment on the use of a uniform benchmark MOE of 30 rather than a benchmark MOE equal to the composite Uncertainty Factors for each study as identified in the 2011 US EPA IRIS assessment for TCE. [Lead Discussant: Melnick]

The use of the factor of 30 for the MOE is reportedly composed of 10 for intraspecies variability and uncertainty and a factor of 3 for the pharmacodynamics portion of the interspecies extrapolation factor. On its face it seems to make sense to me; however, please see my other comments about the MOE.

Question 5-4: Please comment on whether the 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 TCE. Please comment on whether this information is presented in a transparent manner. [Lead Discussant: Portier]

Some of my comments above touch on this question. Indeed, I believe that some of the data limitations are not adequately described especially in the realm of comparing repeat dose hazard benchmarks with acute exposure dosing.

In general, I have not been able to determine from the assessment if there is overlap between the uncertainty associated with the hazard with that of the predicted exposure. I have a reasonable

understanding of the level of uncertainty within the estimation of the exposure potential. For me the largest uncertainty in the exposure piece occurs within the specific inputs of how long, how much and the size of the exposed subpopulations especially for those using TCE-containing products within residences.

Uncertainties within the exposure assessment notwithstanding, the largest gap in the report's transparency for me after reading it and referring to some of the references occurs in the magnitude of the range of uncertainty around hazard. My initial sense was that perhaps much of this inability on my part is caused by my lack of in-depth expertise in the realm of PBPK modeling and the complexity of the analysis; however, my colleagues on the panel who are skilled in the assessment of hazard seemed to have the same issue.

Supplementary comments in response to EPA clarifying questions presented at August 21, 2013, TCE post-meeting

1. *Dr. Jayjock commented that the ventilation rate of 3000 cfm is likely to be a best-case scenario and not typical. The agency used room ventilation rates of 500 cfm and 3000 cfm to represent worst-case and typical ventilation scenarios, respectively. Please provide the agency with values that are representative of worst-case, typical and best-case scenarios for ventilation rates at facilities using TCE in degreasing operations? Regarding facility size (e.g., room volume), please provide the agency with values that are representative of facilities using TCE in degreasing operations. Where possible, please provide the supporting reference(s).*

My primary reasons for stating that 3000 cfm is likely a best-case scenario are presented in my original report. During my tenure as an industrial hygienist and risk assessor for a major chemical company I had the opportunity to study and sometimes measure mixing air changes in large and small industrial rooms. My experience and recollection is that these room had rates in the range of 2 to 6 air changes per hour IF they were not situated in hot industries (e.g., steel mill) or volumes with a purposely high level of local exhaust ventilation (e.g., laboratories). Some of these were measured rates and some were based on review of ventilation design. I do not have access to these data and indeed they probably no longer exist.

I have searched the literature for many years and have not been able to locate good comprehensive data on levels of ventilation extant within industrial rooms. When data are lacking one must rely on their judgment and experience. This is what I did for these particular comments.

2. *Dr. Jayjock commented that the subpopulation of workers potentially exposed to TCE needed to be quantified. Please refer to a) Table 3-8 and the preceding paragraphs in the TCE risk assessment and b) slides 30 and 31 of the presentation that EPA presented during the July 9, 2013 peer review meeting. Based on your experiences, please provide the agency with alternative estimates for the number of workers potentially exposed. Where possible, please provide the supporting reference(s).*

Upon further review of the items mentioned above it would appear that 5 workers per facility in about 23,000 facilities is a reasonable estimation of the subpopulation. I apologize for the oversight.

3. *Dr. Jayjock recommended that the agency substantiate that dermal exposure is indeed negligible compared to potential exposures via the inhalation route. Based on your professional judgement, please provide the agency with recommended values for the diffusion/permeability coefficient of pure TCE through human skin. Where possible, please provide the supporting reference(s).*

In the EPA Toxicological Review of Trichloroethylene Chapter 3 for IRIS (2011) (EPA/635/R-09/011F) there is the following passage:

> "With respect to dermal penetration of liquid TCE, Nakai et al. (1999) used surgically removed skin samples exposed to TCE in aqueous solution in a chamber designed to measure the difference between incoming and outgoing [^{14}C]-TCE. The in vitro permeability constant calculated by these researchers averaged 0.12 cm/hour."

The book: Water Contamination and Health, Rhoda G.M. Wang, ISBN: 0-8247-8922-9, 1994, p 343 found in a Google book search indicates an experimental value in hairless live Guinea Pigs of 0.23 cm/hr.
(http://books.google.com/books?id=xCruHfytXZYC&pg=PA324&lpg=PA324&dq=dermal+permeability+constant+tce&source=bl&ots=wdqH97ai4u&sig=W5apk22NlxWovWIS5_iWKa1awow&hl=en&sa=X&ei=ebsUUomvOYSdyQGr3oGoCQ&sqi=2&ved=0CGUQ6AEwBw#v=onepage&q=dermal%20permeability%20constant%20tce&f=false)

Given these result my opinion is that the *in-vitro* human data would provide the best value to use because of known interspecies differences in dermal penetration.

The above results were the result of a rather brief search. A more extensive Google search would possibly render considerably more data on the dermal penetration rate of TCE.

Clarifying Questions for the Consumer Exposure Assessment

The first two questions are based on comments from Dr. Jayjock:

1. *Please provide references for assessments on highly volatile chemicals that developed and compared estimates for the dermal and inhalation exposure pathways.*

A primary example of an assessment of a VOC that included and compared inhalation and dermal exposure assessment is presented in the EPA's Voluntary Children's Chemical Evaluation Program (VCCEP) Submission for methyl ethyl ketone (CAS NO. 78-93-3). Ref:
http://www.tera.org/peer/VCCEP/MEK/MEK%20VCCEP%20Submission%20December%202003.pdf

A more recent example is contained in Health Canada's draft screening assessment for the even more highly volatile chemical: acetone. Ref: Draft Screening Assessment for Acetone, Chemical Abstracts Service Registry (CAS 67-64-1), Environment Canada, Health Canada, July 2013.
http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=CB62CB1D-1#toc23

Health Canada has performed scores of preliminary risk assessments on VOCs that include dermal and inhalation exposure. References for these should be available on the Internet.

2. *Please provide references for assessments that have implemented personal breathing zone calculations and/or eddy diffusivity modeling that could contribute to OPPT's exposure assessment of TCE emissions from degreaser and arts/crafts products.*

I am not aware of any such references. Indeed, as mentioned in my comments, eddy diffusivity modeling has not been used much here-to-fore because of the difficulty in the estimation of the eddy diffusivity coefficient. The most highly vetted near-field model is the Nicas 2-zone model and the following

reference summarizes much of the work comparing breathing zone and model predictions. Ref: Jayjock, M.A., T.W. Armstrong, M. Taylor: The Daubert Standard as Applied to Exposure Assessment Modeling Using the Two-Zone (NF/FF) Model Estimation of Indoor Air Breathing Zone Concentration as an Example, Journal of Occupational and Environmental Hygiene, November 2011, 8: D114–D122 ISSN: 1545-9624 print / 1545-9632 online**.** My suggestion is merely to include the eddy diffusivity modeling for comparison with the near-field Nicas two zone modeling. If it is determined to do only one type of model then my advice would be to use the Nicas model.

References

[i] Keil, C.B., C.E. Simmons, and T Renee Anthony (eds): Mathematical Models for Estimating Occupational Exposure to Chemicals, AIHA Press, 2009**.**

[ii] National Institute for Health and Environment ()RIVM, Netherlands: http://www.rivm.nl/en/Topics/C/ConsExpo Last accessed July 18 2013.

[iii] National Academy of Science: Clearing the Air: Asthma and Indoor Air Exposures, Committee on the Assessment of Asthma and Indoor Air, Division of Health Promotion and Disease Prevention, p. 410, ISBN: 0-309-51861-X, 456 pages, 6 x 9, (2000).

[iv] Charles B. Keil, C.B. and Mark Nicas: Predicting Room Vapor Concentrations Due to Spills of Organic Solvents, AIHA Journal 64:445–454 (2003).

[v] Kai-Chung Cheng, V. Acevedo-Bolton, Ruo-Ting Jiang, Neil E. Klepeis, Wayne R. Ott, Oliver B. Fringer, and Lynn M. Hildemann: Modeling Exposure Close to Air Pollution Sources in Naturally Ventilated Residences: Association of Turbulent Diffusion Coefficient with Air Change Rate, Environ. Sci. Technol. 2011, 45, 4016-4022.

[vi] AIHA Exposure Strategies Committee: http://www.aiha.org/get-involved/VolunteerGroups/Pages/Exposure-Assessment-Strategies-Committee.aspx, last accessed July 10 2013.

[vii] US EPA (2011c). Toxicological review of trichloroethylene (CAS No. 79-01-6). In support of summary information on the Integrated Risk Information System (IRIS). US Environmental Protection Agency, Integrated Risk Information System, Washington, DC. http://www.epa.gov/iris/supdocs/0199index.html. Accessed November 7, 2012. EPA/635/R-09/011F.

Kenneth Portier

Question 4-2: Please comment on the <u>strengths and weaknesses</u> of using multiple values for each type of adverse effect.

I struggled with how to answer this question.

Page 56 in the report states:

> "Rather than use a single, point estimate value for the non-cancer risk assessment, a range of risk estimates are presented, thereby providing a range of data. This allows flexibility in evaluating or estimating risk based on exposure duration."

Appendix F contains a detailed table of all 32 different candidate PODs/HECs developed by the IRIS program, with the 17 inhalation studies used in the assessment listed in Table 3-17. Of these 17, 9 are from studies with multiple doses, 8 from single dose studies. Table 3-19 contains summarizes the inhalation study values from Appendix F by target organ and exposure duration.

If I have understood this section correctly, there is actually much less data available that it would seem at first glance of Table 3-19. For any one combination of target organ there are at most four separate values, and these values may not all relate to the same actual effect. For example, the chronic/liver adverse effect data, from Appendix F, actually comes from only two studies. Hence the range is defined by these two studies. Note that one of these studies in in mice and the other in rats.

So, how has this assessment actually used multiple values to introduce "flexibility". Primarily, the multiple POD values have allowed EPA to examine MOE across a set of "scenarios" other than just the "worst case". These scenarios are generated by using different combinations of value from the range of HEC50 and HEC99 values for each exposure category. Results of this assessment is given in Table 3-26 and discussed on pages 67-68. Note that Table 3-26 can be confusing unless one reads the footnotes carefully. A YES in this table indicates a change from "potential risk" to "no risk", a very different interpretation than a YES in Table 3-25.

How have these multiple scenarios been used? The whole alternate scenario effort is summarized on page 72.

> "As shown in Table 3-26, using different HEC_{50} and HEC_{99} values does change the risk picture somewhat for some exposure scenarios; primarily eliminating acute effect risk concerns for neurotoxicity for consumer users and non-users of both the degreaser and clear protective coating spray scenarios. However, regardless of the hazard value used within the bounds identified in this assessment, chronic effects concerns continue to exist for the small commercial worker for most scenarios, and for all scenarios with kidney toxicity as the endpoint of concern."

This statement leads me conjecture that regardless of the alternate scenario results, the worst case results will tend to drive conclusions, suggesting that there may be little benefit to this alternate scenario.

In conclusion, the strength of using multiple POD values lies in allowing the assessment to explore in more detail multiple outcomes under different exposure scenarios (Table 3.21). The weakness of using multiple POD values is that time and effort is spent on generating results that may not really impact the

final conclusions beyond what was obtained by looking at the worst case scenario. This is not to say that this exercise is not without merit. Clearly keeping multiple effects in the discussion throughout the document increases the perception that these assessment did not focus down on one health effect too early in the process. In addition, it is possible that the results of a sensitivity analysis (for either or both of exposure and hazard) could point to more than one health effect having to be accounted for in the final conclusions.

Transparency and readability of the report would be improved by combining Table F-1 with Table 3-19. This will reduce the burden on the reader to constantly shift between the two tables during reading.

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

This questions asks whether the uncertainty and data limitation discussion in the report is both adequate and transparent (readily understood).

I felt that the section of the report where uncertainties are discussed was well written. The authors are attempting to point out limitations of data and assumptions that could bias results. There are a couple of areas where a little more discussion will improve transparency.

Statistician typically have difficulty with phrases such as "medium to high degree of confidence" because these are qualitative assessments rather than quantitative likelihood estimates. It would help if these assessment levels were better defined. What generates "high degree of confidence" in an estimate or model input or output?

On page 71 we are informed that "Virtually all of the information on TCE hazard for this risk assessment was taken from the recent IRIS publication…" I did not see any hazard information that did not originate from this publication.

The discussion on page 71 which talks about why EPA chose to not use the RfC or RfD values generated for the inhalation studies is not adequate.

> "In developing an RfC or RfD, uncertainty is captured by the use of uncertainty factors (UFs). Depending on the POD, UFs of between 10 and 1,000 were used to derive candidate RfD/RfCs. In this risk assessment, rather than using a single value (i.e., the RfC) to evaluate inhalation exposures for the scenarios identified, it was decided to evaluate the range of data evaluated by the IRIS program to derive the RfC."

A lot of time and effort went into generating RfC/RfD values for each study by effect combination in the IRIS assessment. In particular, a lot of thought went into what was the appropriate UF for each case. Why exactly does this assessment revert back to PODs and utilize an MOE?

At the end of page 71 we have the statement: "By focusing only on inhalation studies and using lower-end HEC_{99} values, OPPT has increased the likelihood that risks are not under-estimated." So, just how conservative are these estimates? My own personal preference in a data-rich environment is to utilize probabilistic risk assessment methodologies where we can address quantitatively the issue of degree of conservativeness. Could probabilistic risk assessment be used for this assessment and why not?

I am not sure what to conclude from the discussion in the section titled “Uncertainties in the Risk Assessment”. The point of this discussion seems to be the conclusion that exposure estimates express small variation but may be biased high or low, while at the same time the hazard values are very variable. As a result, the overall risk assessment conclusions may be more dependent on which specific hazard value is used.

As I re-read this section, I wondered if it would help to separate the concepts of variability and uncertainty in the discussion. Exposure and hazard estimates can be both uncertain and variable. Uncertainty relates to precision of estimation. Variability typically relates to how the true value changes within a population. The uncertainty sections seem to jump between these two concepts.

Finally, there was much discussion before the Panel about the need to include a sensitivity analysis for both the exposure and hazard parts of the risk value estimation. On the hazard side, the SAB panel that reviewed the IRIS assessment and in particular the PBPK model recommended more sensitivity analysis of the model parameters be performed. The analysis that was performed indicated that model results (estimates) were not particularly sensitive to small perturbations of parameters. This suggests, as was pointed out in the Panel discussions, that more effort be placed on decreasing uncertainty on the exposure side of the equation.

Ron Melnick

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

This document relies heavily on toxicity information from EPA's 2011 IRIS review of trichloroethylene. Although it is appropriate to apply results from the IRIS review of TCE in this risk assessment, it is important that justification for use of those results is clearly communicated in the OPPT document—some examples of where further clarification would be helpful are noted in subsequent parts of this review.

The TCE risk assessment for non-cancer endpoints is based solely on results from inhalation studies. In contrast, the IRIS review derived an RfC based on findings from oral studies using a PBPK model to perform route-to-route extrapolation of results. The estimated RfC is 0.0004 ppm. The current TCE risk assessment should note that the IRIS RfC for TCE (0.0004 ppm) is similar to the most sensitive hazard value from inhalation studies (HEC99 of 0.013 ppm for kidney effects) divided by an MOE of 30. This comparison adds confidence to the current assessment, but does not justify excluding results from oral studies in this assessment. This assessment would benefit if hazards of TCE from the oral route of exposure were also included (see response to Question 4-3 below).

By not including dermal exposure in the exposure assessment, internal doses are likely to be underestimated. The document recognizes this deficiency (page 71) and notes that TCE is rapidly absorbed in humans following dermal exposure (page 35), but claims that the use of the lower-end HEC99 values provides a counterweight to not considering dermal exposure. That is a poor excuse for excluding this potentially relevant route of exposure. The assessment does not provide data to justify the claim that dermal exposure is "less significant" (page 14) and ignore this exposure pathway in the risk assessment. To justify excluding the dermal route of exposure in this assessment, some attempt must be made to estimate the extent of dermal exposure compared to inhalation exposure among degreasers and hobbyists using products containing TCE (e.g., the model used to estimate inhalation exposure by the hobbyist degreaser or clear protective coating spray provides a means to estimate dermal exposure).

The TCE risk assessment refers to the HEC99 value as the human equivalent exposure concentration for the "sensitive" human; however, in EPA's IRIS document, the HEC99 is defined as an exposure for which there is 99% likelihood that a randomly selected individual will have an internal dose less than rodent internal dose at the POD for each critical effect. Thus, the HEC99 value does not represent the "sensitive" human because it does not account for pharmacodynamic variability in the human population. Furthermore, the HEC99 is based only the range of human parameters entered into the PBPK model that provided this value, and may not represent the lower 99th percentile of human pharmacokinetic variability.

Qustion 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 characterization.

In the inhalation studies that provided the lowest HEC_{99} for the kidney (Woolhiser et al., 2006) and reproductive system (Chia et al., 1996), EPA's 2011 IRIS review provided statements of concern. Kidney: Woolhiser et al. (2006). "the small number of animals and the variation in initial animal weight limit the ability of this study to determine statistically significant increases." Reproductive system: Chia et al. (1996). "Mean exposure estimates for the exposure groups were limited because they were defined in terms of ranges and because they were based on mean urinary TCA" and "there is substantial uncertainty

in the conversion of urinary TCA to TCE exposure level". "In addition, there was uncertainty about the adversity of the effect [hyperzoospermia] being measured". The TCE assessment needs to provide justification for why these studies were selected for the MOE analysis in light of these uncertainties/limitations.

EPA identifies TCE as "carcinogenic to humans by all routes of exposure." The designation "probable human carcinogen" on pages 10 and 13 is outdated and needs to be corrected. On page 12 (second bullet), the statement that cancer risks were all "below" the benchmark values should be changed to "above."

References

For completeness, the following references should be noted in this assessment:

Hosgood HD III, Zhang L, Tang X, Vermeulen R, Qiu C, Shen M, et al. 2011. Decreased numbers of CD4+ naive and effector memory T cells, and CD8+ naive T cells, are associated with trichloroethylene exposure. *Front Oncol* 1:53; doi:10.3389/fonc.2011.00053 [Online 10 January 2012].

Karami S, Lan Q, Rothman N, Stewart PA, Lee KM, Vermeulen R, et al. 2012. Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis. *Occup Environ Med* 69:858–867.

Karami S, Bassig B, Stewart PA, Lee KM, Rothman N, et al. 2013. Occupational trichloroethylene exposure and risk of lymphatic and haematopoietic cancers:a meta-analysis. *Occup Environ Med* [ONLINE MAY 30, 2013].

Vermeulen R, Zhang L, Spierenburg A, Tang X, Bonventre JV, Reiss B, et al. 2012. Elevated urinary levels of kidney injury molecule-1 among Chinese factory workers exposed to trichloroethylene. *Carcinogenesis* 33:1538–1541.

Zhang L, Bassig BA, Mora JL, Vermeulen R, Ge Y, et al. 2013. Alterations in serum immunoglobulin levels in workers occupationally exposed to trichloroethylene. *Carcinogenesis* 34:799-802.

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 the workplace exposure assessment, including estimations for bystander/non-users (e.g., women of childbearing age).

In estimating inhalation exposures for workers and bystanders (Appendix D), a two-zone air model was used that includes discrete compartments for near field and far field exposures. Because bystanders may be present in the same room as the TCE emitting source, alternative models (e.g., 1-compartment evaporation and diffusion model) should also be considered for estimating concentrations of TCE in far-field locations. Does the model predict uniform concentrations of TCE in the far field or do gradients exist in this compartment? This is important because gradients would impact exposures for bystanders based on their distance from the generating source.

Describe how the local exhaust ventilation (LEV) affects the generation rate. Discuss the reliability of the assumption that LEV reduces TCE emissions by 90%. Wadden et al. (1989) estimated the emission rate for TCE from commercial degreasers fitted with a local exhaust hood to be 2.6 g/min for an open-top degreaser and 0.67 g/min for an enclosed degreaser. Why was a single value of 1.67 g/min used as the emission rate for TCE with LEV?

A weakness of the OPPT document is that it provides no information on attempts to validate model predictions with experimental data. The reference to ATSDR (1997) for support of the estimated

workplace exposure concentrations is inadequate, since that document contains no more information on the TCE worker exposure data than the one sentence given in Appendix D. The EU Risk Assessment for TCE (EC, 2004), which is also cited in Appendix D, only provides a claimed "reasonable worst-case exposure levels" (50 ppm for metal degreasing expressed as a 8-hour TWA). Both of these references are inadequate to validate model-based estimates of TCE exposure TCE by workers and bystanders, e.g., neither reference specifies whether or not the exposures were based on local exhaust ventilation.

Validation of model predictions of near-field and far-field exposure concentrations for TCE or other volatile solvents would significantly reduce uncertainties in the exposure assessment. Jayjock et al. (*J Occ Environ Hyg* 8:D114-22, 2011) have shown that the performance of the two-zone near field/far field indoor air model used in the TCE risk assessment is remarkable in simulating near field air concentrations for several volatile contaminants and is therefore reasonably reliable in predicting workplace exposure levels. This type of information must be highlighted in the TCE risk assessment because it supports the use of the OPPT document as more than a screening level assessment.

Question 3-1: Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models, or information (*e.g.*, information on duration and number of user events) that could be considered by the agency in developing the exposure assumptions and estimates for the hobbyist degreaser and clear protective coating spray uses, and for the bystander/non-users (e.g., children, women of childbearing age).

Similar to my comments above for model-based estimates of workplace exposure to TCE, I am concerned that there was no mention of any attempts to validate hypothetical exposure estimates for users (and bystanders) of aerosol spray products containing TCE or of other volatile solvents with physical/chemical properties similar to TCE. Any validation of model predictions should be noted in this assessment because it would add confidence to the model-based exposure estimates and would allow reasonable exposure estimates for other circumstances, e.g., larger house, different air flow rates between rooms, etc. Thus, while the approach used in the TCE assessment seems reasonable, there is no way to evaluate the reliability of the model-based exposure estimates.

The approach for estimating air concentrations of TCE from aerosol spray products seems to be a bit convoluted – a model is used to estimate the potential acute dose rate (ADRpot), which is then used to calculate the air concentration of TCE that led to that parameter. Since the model allows estimation of dermal exposure, that calculation should be included in the estimation of the ADRpot. All model assumptions need to be explicit, e.g., ventilation in the room of use. Were other models considered (e.g., evaporation and diffusion model) and if so did they provide similar results as the model used in this assessment? Why aren't air concentrations estimated from parameters that affect levels of TCE in the breathing zone of the user (e.g., vapor pressure, air exchange rate) and then validated with experimental data? A serious weakness of this exposure assessment is the lack of any validation of the hypothetical exposure estimates.

Question 4-1: Please comment on the strengths and weaknesses of evaluating different endpoints based on exposure durations (*i*.e., acute versus chronic).

Evaluating different endpoints based on acute versus chronic exposures is appropriate if the development of the adverse effect is a consequence of that exposure duration. A strength of evaluating an endpoint based on comparable exposure duration is that an additional adjustment factor would not be needed if only acute exposure data were available. However, if the progression or severity of an endpoint increases with chronic exposure, it would not be appropriate to assess the risk of that effect after only short-term

exposures. If only acute exposure data were available for a condition that worsens with chronic exposure, then an additional adjustment factor would be needed to account for the reduced exposure duration.

A weakness of this approach in the OPPT risk assessment for TCE is that chemically induced neurotoxicity is not necessarily a result of only acute exposures. OPPT has not provided evidence showing that the development and progression of neurodegenerative diseases are limited to acute exposure conditions. As noted in the TCE risk assessment, neurotoxicity has been observed in animal studies and in humans after acute and chronic exposure conditions. Similarly, in target organs linked to chronic exposures (liver, kidney, reproductive toxicity, and immunotoxicity) adverse effects were identified after exposures of 4 weeks or less. For toxicological endpoints that can occur after acute or chronic exposures, health risks should be assessed for both short-term and chronic exposure durations.

Question 4-2: Please comment on the strengths and weaknesses of using multiple values for each type of adverse effect.

The strength of using multiple values for each type of effect is that the relationship between exposure and all identified potential target organ effects for workers and consumers exposed to TCE are presented in a transparent manner for the risk manager. The range of values for each target organ may reflect consistency or inconsistency in potency estimates for an evaluated effect between species or differences in sensitivity for specific target organ endpoints.

The weakness of using multiple values for each target organ is that the underlying reasons for the range of values are not provided. This shortcoming might lead to a misinterpretation of the data and the analyses performed by OPPT. For example, the risk manager or others may interpret the selection of the lowest HEC99 value as EPA being overly conservative in its risk assessment, while the selected POD may actually represent the evaluation and detection of a more sensitive endpoint in the target organ.

Question 4-3: PBPK modeling was employed in the 2011 IRIS assessment for route-to-route extrapolation to develop a corresponding inhalation value from oral studies, some of which involved endpoints not studied or reported in inhalation studies. OPPT supports the approach used in the IRIS assessment. However, OPPT did not use PBPK-derived human-equivalent concentrations from oral studies in the current draft risk assessment, because OPPT focused on a narrow set of TCE consumer uses (e.g., degreasing and arts/crafts uses) that are subject to TSCA and therefore, OPPT's draft risk assessment relied only on inhalation exposure studies that directly mimicked inhalation exposure use scenarios for both adults and developmental life stages. Please comment on whether the 2011 IRIS assessment's PBPK-derived inhalation values from oral studies should be used in the final OPPT risk assessment.

The only apparent criterion used to select PODs for the MOE analyses was that the studies involved inhalation exposures. Additional justification is needed for not including oral studies and conducting route-to-route extrapolations of results. In the IRIS review of TCE, EPA derived an RfC based on findings from oral studies using a PBPK model to perform route-to-route extrapolation of results. A comparison of the lowest HEC_{99} values, expressed in ppm, is shown below for the target organ effects observed in inhalation studies that were included in this assessment and values derived from oral studies using the PBPK model to provide route-to-route extrapolation. These comparisons support the inclusion of HEC values derived from oral studies in the OPPT risk assessment because:

1. for liver, kidney, and neurotoxicity the HEC values are comparable reinforcing the inhalation derived values,

2. for immunotoxicity and developmental toxicity the inhalation derived values are substantially higher than the oral derived values indicating that risks for these target systems might be underestimated if based on the limited number of inhalation studies that evaluated health effects in these systems, and

3. for reproductive toxicity the oral derived HEC was much higher than the inhalation derived value; however, because the inhalation study was based on sperm effects in men while the oral study is based on decreased *in vitro* fertilization for male rats, the lower value from the inhalation study may reflect the greater sensitivity of humans to reproductive effects of TCE.

Target organ	Route of exposure	HEC_{99} (ppm)	Reference
Liver	Inhalation	9.1	Kjellstrand et al, 1983
	Oral	11	Woolhiser et al, 2006
Kidney	Inhalation	0.013	Woolhiser et al, 2006
	Oral	0.0056	NTP, 1988
Neurotoxicity	Inhalation	4.8	Arito et al, 1994
	Oral	7.1	Isaacson et al, 1990
Immunotoxicity	Inhalation	11	Woolhiser et al, 2006
	Oral	0.033 1.7	Keil et al, 2009 Sanders et al, 1982
Reproductive toxicity	Inhalation	0.5	Chia et al, 1996
	Oral	9.3	DuTeaux et al, 2004
Developmental toxicity	Inhalation	6.2	Healy et al, 1982
	Oral	0.0037 3	Johnson et al, 2003 Fredriksson et al, 1993

Some discussion is also needed on how PODs were determined, particularly for studies with a control group and a single TCE dosed group. For example, in the developmental study by Healy et al. (1982), the only concentration tested was 100 ppm, yet a LOAEL = 17 ppm was identified as the POD. What assumptions, beyond adjustment to continuous exposure, were made in estimating this POD?

Question 5-1: Please comment on the strengths and weaknesses of the MOE approach used to estimate the chronic, non-cancer risk for the workplace exposures; including non- users.

The MOE approach provides a meaningful signal of concern for several non-cancer health effects that might be caused by TCE in workers and bystanders exposed to this chemical. The approach relies on information of TCE's hazards from EPA's IRIS review and estimations of worker exposure in this TCE risk assessment. Aside from issues related to the assessment for workplace exposures (including non-users) and estimations of hazard values discussed above, the MOE approach seems appropriate. The strengths and weaknesses of this approach are a function of the reliability of the two parameters that produce the MOE. The assumption of chronic exposure to TCE for the workplace degreaser is appropriate. The workplace TCE exposures are based on an 8-hour TWA, presumably for 5 days per week. However, the POD hazard values were adjusted in the IRIS program to continuous exposure. Thus, the worker exposure value should likewise be adjusted to continuous exposure.

Selecting a benchmark MOE of 30, as a unique value that can distinguish risk from "no potential risk of concern" requires that the uncertainties surrounding the exposure and hazard values have been accurately quantified. I don't believe this to be the case. Thus, an MOE greater than 30 may indicate lesser concern than an MOE < 30, but does not establish "no potential risk of concern." The exclusion of dermal exposure as a contributor to the internalized dose of TCE has not been adequately justified in this assessment. The assumptions used to support the conclusion that dermal exposure is not significant need to be tested with TCE or referenced to a validated exposure assessment of a solvent with similar physical/chemical properties.

Question 5-2: Please comment on the strengths and weaknesses of the MOE approach used to estimate the acute risk to consumers; including non-users (e.g., children, women of childbearing age). Specifically, please comment on the decision to limit the analysis to acute exposures without residual concern between events (*i.e.*, once/week for users of the clear protective coating spray, and twice/month for degreaser users).

Similar to my response in 5-1, the MOE approach provides a meaningful signal of concern for several non-cancer health effects that might be caused by TCE in consumers and bystanders exposed to this chemical. I have no basis for commenting on several input parameters, e.g., whether consumer exposures are likely to occur once/week for users of clear protective coating spray and twice/month for degreaser users. Perhaps a distribution of frequencies and durations of use should be included in these model-based exposure estimates. The assumption that consumer use of degreaser sprays and clear protective coating spray is intermittent and that there is likely little residual concern for TCE or its metabolites between events seems reasonable. A weakness of the approach is the assumption that there is no chronic exposure concern for hobbyist degreasers and clear protective spray users (Table 3-20) because the use of consumer products is infrequent and that there would be insignificant residual TCE or its metabolites in users or bystanders between events. However, the supplemental information on E-FAST CEM outputs includes repeated exposures over a 57-year period for users in these scenarios and exposures may begin in utero and occur at a very early age for bystanders. Consequently, there may be may be a concern for potential chronic health effects, particularly cancer risk, among consumers who use products containing TCE. Thus, I recommend that assessments of potential cancer risk be conducted for hobbyist consumers, bystanders, and hobbyist consumers who had been exposed previously as bystanders (in utero and as children). Similar to my comment above for workplace exposures, the exclusion of dermal exposure as a contributor to the internalized dose of TCE has not been adequately justified in this assessment. Lastly, acute risks should also be assessed for adverse effects that were observed in the liver or kidney of experimental animals after 4 weeks or less of exposure.

Question 5-3: Please comment on the use of a uniform benchmark MOE of 30 rather than a benchmark MOE equal to the composite Uncertainty Factors for each study as identified in the 2011 US EPA IRIS assessment for TCE.

This risk assessment should provide a fuller description of what is uncertain in the exposure and hazard assessments. The use of a uniform benchmark MOE of 30 for all endpoints has not been justified. This value was based on a factor of 3 for extrapolating data from animal studies to humans and 10x for intraspecies differences within the human population. Because a model was used to extrapolate an internal dose in animals to a concentration that provides a human equivalent dose (HEC), the interspecies uncertainty factor of 3 was used to account for possible pharmacodynamics difference. EPA needs to explain why a factor of 10 was used for intraspecies variability in light of the fact that an HEC99 was used as the POD hazard value. The HEC99 is expected to account for the pharmacokinetic portion (3X) of the 10X factor that is typically applied for intraspecies variability. However, because the HEC99 value is

a function of the range of variability of human parameters entered into the PBPK model, it is not clear whether or not it truly captures the lower 99th percentile of the human population for the concentration of TCE that leads to an internal dose in humans equivalent to the rodent internal dose. Based on the relatively narrow range of human metabolic parameters used in the PBPK model (obtained from only 42 adults), it is likely that the model did not capture the full range of interindividual variability due to genetic polymorphisms in metabolizing genes, age, gender, and extrinsic factors that affect levels of gene expression. The selection of an appropriate uncertainty factor for intraspecies variability needs to be fully addressed in the OPPT risk assessment.

For assessments of health effects that were based on LOAELS instead of BMDLs (neurotoxicity and developmental toxicity), an additional uncertainty factor may need to be applied. For assessments of chronic health effects that were based on studies of short duration (e.g., liver toxicity, immunotoxicity,), an additional adjustment factor needs to be applied for the reduced exposure duration. Thus, it is not appropriate to assess non-cancer risks with a benchmark MOE of 30 for all candidate effects. To justify a uniform MOE, the assessment would need to provide an adequate explanation on why this value is applicable to all critical studies regardless of differences in how the POD was estimated (LOAEL versus BMDL) and why an additional adjustment was not needed to assess chronic health risks from short duration studies. Lastly, no adjustment factor was applied for the uncertainties in the exposure assessments. The above issues reduce confidence in the use of a uniform benchmark MOE of 30.

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

A strength of this assessment that should be highlighted is that the inhalation unit cancer risk for TCE was based on human kidney cancer data.

Possibly because this document relies so heavily on toxicity information from EPA's 2011 IRIS review of trichloroethylene, it does not adequately communicate uncertainties in the non-cancer health hazard data in an adequately transparent manner. For example, as noted above, the TCE risk assessment does not address concerns raised in the IRIS review about the utility of the data by Woolhiser et al. (2006) and by Chia et al. (1996). My comments above concerning the exclusion of dermal exposure in this assessment are also noted in the section on uncertainty and data limitations. However, the document offers no solutions to address this issue other than to claim that the HEC99 "can provide a counterweight to not considering dermal exposure."

A metabolic scheme with indication of metabolites and/or pathways that were used in the dose-response analyses would be helpful. In addition, a strong justification for the selected dose metrics should be provided in the text. For example, I am not convinced that the amount of TCE oxidized in the liver is an appropriate dose metric for liver cancer and non-cancer liver effects because it does not include essential information on the clearance of metabolites that contribute to liver cancer or toxicity. Simply noting that this was done for the IRIS review is not a satisfactory explanation and does not reduce uncertainties in the estimated HEC99 values.

BMDL needs to be defined. In the IRIS review, BMDL is the (one-sided) 95% lower confidence bound on the dose corresponding to the benchmark response for the effect (i.e., the lowest dose level that can be supported by modeling the data). The benchmark response rate(s) used in this assessment should be

specified. The reliability of BMDL values derived from single dose studies or studies of questionable quality should be addressed in the section on sources of uncertainty and data limitations.

While recognizing that there are uncertainties in the exposure assessment and that "assumptions were not extensively evaluated," no adjustment was made in the MOE analysis to account for this uncertainty. The fact that the exposure assessments for consumers were based on models that had not been validated raises uncertainty in the exposure values used in this assessment. This uncertainty could be reduced if evidence was provided showing that the exposure models had been validated with solvents having chemical and physical properties similar to TCE.

Supplementary comments in response to EPA clarifying questions presented at August 21, 2013, TCE post-meeting

Based on panel discussions on whether or not the TCE workplan assessment is adequate for regulatory purposes or should be considered simply as a screening-level assessment, the document should emphasize the fact that TCE has been shown to cause toxicity in multiple organs of humans and that both USEPA and IARC have classified TCE as a human carcinogen. Furthermore, the inhalation unit cancer risk reported in EPA's 2011 IRIS review of TCE is based on human kidney cancer data. Thus, regulatory action is urgently needed to protect humans exposed to this agent in the workplace or in their residence. If OPPT anticipates significant delays in improving the exposure assessment for more accurate assessment of health risks for bystanders and hobbyists, then regulatory actions should be implemented with required workplace monitoring and consumer warnings based on both the IRIS RfC and the estimated inhalation cancer risk. The model-based estimates of workplace exposure for degreasers are reliable for regulatory purposes.

Barry Ryan

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

In my opinion, EPA has performed a detailed analysis of the problem at hand but has failed to present it in a clear and concise fashion. As discussed under Question 1-2, many of the assumptions used are stated without reference and appear somewhat arbitrary or *ad hoc*. While it may be that neither of these is indeed the case, it is difficult for the reader to grasp the motivation for some of the parameter selections and hence transparency is lost. Further, the impact of alternative selections for modeling parameters is not clearly delineated through, for example, sensitivity analysis. It may well be that the ultimate outcome of the document, namely a screening risk analysis associated with various exposure scenarios, is not strongly affected by the choice of these parameters, but the reader is not privy to such information since it is not presented.

I think the document would be substantially improved if a clear statement was made regarding the audience for the report. Is this, for example, a report that would be used by technically proficient risk modelers in the pursuit of their work? If so, perhaps it is sufficient. But, I believe, by its very nature it seems unlikely that such a document would be ignored by a more general audience. Under this scenario, much more detail into the reasoning must be present to ensure clarity of presentation and understanding by a less technical group of readers. This would begin with a clear and unambiguous statement of the content and expected utility of this document in the first few pages. This would be followed using essentially the same outline as is currently present but expanding each section to explain more fully what the selection criteria were for various modeling parameters, inclusion criteria for manuscripts and documents, and likely effects associated with alternative modeling strategies. At such a point, the document would be much more transparent.

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 characterization.

While the literature cited is useful, there does not seem to be an exhaustive effort made to find all existing appropriate literature for the various sections. Several statements are made to the effect that few if any data exist on the topics at hand- small-scale degreasing operations and hobbyist uses of TCE and TCE-containing materials. Yet much of the "occupational" literature is directly applicable to the small-scale operations as it is to the large-scale degreasing facilities. Indeed, application of such data is used throughout. Emission characteristic are similar for both open and closed systems as well as for systems using local exhaust ventilation. Exposures to individuals are likely similar. It was interesting to note that the work of Wadden, et al., done in the late 1980s and EPA's work were compared and found to give similar results for large facilities (See Table 3.7). The Wadden results are also compared for smaller facilities. EPA's results suggest a three-fold decrease in emissions from smaller facilities. It is unclear what supports this decrease, which is, of course, crucial in determining the ultimate concentrations and thus exposures received by both workers in such facilities and by-standers. A more thorough discussion of this with appropriate references should be included. Further, scenarios common in the 1980s, which may have included ineffective ventilation systems, whole-building ventilation, or poor local exhaust ventilation (LEV) may result in different estimates in 2013. While the Wadden, et al., work was well done, it is now 25 years later. More literature is available and should be explored.

Little work has been done on hobbyists TCE exposure to my knowledge. However, exposure measurements on other hobbyist material, e.g., lead exposure among stained-glass hobbyists, or other VOC-related activities, has been done and could serve for as a better model. I saw no references to the literature that followed this approach. The utility of such work lies not only in the direct measurement of the exposures experienced by such individuals, but also in affording better parameterizations of the models (see Discussions below.) Use of such data, or at least the discussion of such, would support the approach used. If no such data are available, EPA could easily perform chamber experiments to evaluate, for example, the amount of TCE-containing spray used in a given application, and determine use patterns, e.g., is the 28 g per application and a 30-minute application once every two weeks at all associated with real-world use as discussed in the following paragraphs.

Specific comment regarding the choice of modeling scenarios:

The choice of modeling conditions and, in particular, the emission parameters and flow rates between compartments appear to be quite arbitrarily set and not well documented or referenced. Further, it is difficult to find the parameter used as they are scattered among several sections. A single table describing parameters for both the small-scale degreasing facilities and the hobbyist exposure scenarios would be well placed in Chapter 3 somewhere. Otherwise one has to examine both that Chapter and Supplemental materials to assess the quality of the model inputs. I would like to see EPA make a better effort in justifying the specific emission rates for hobbyist type crafts and for the emissions associated with the use of TCE-containing materials. For example, through a series of assumptions, e.g., one can of aerosol degreaser per year, etc. (See Supplemental Degreaser Document), EPA has come up with an emission rate for TCE in hobbyist activities To my mind, these emission rates, which strongly affect exposures and risk, are quite arbitrary and supported by very few data. Essentially all parameters used in these models- emissions, durations, air flows etc., are poorly justified and have the appearance of *ad hoc* and arbitrary assumptions. Yet the values are critical in understanding the risk. Admittedly, few data are available, as has been pointed out by EPA, but in such circumstances, it become incumbent upon the modeler, and EPA in general, to produce full text describing the reasoning. Are there data to support the “one can a year” used at regular intervals? How does this really jibe with hobbyist use? How about the duration of the exposure- 30 minutes? Are there data to support this? I know of none, but perhaps EPA does and therefore must reference it. If no such data exit, justification of the scenario and what its utility might be is necessary. Do these represent typical, worst case, or some other percentile of the exposure distribution? Again, these are screening levels, but we need *some* context for our discussion.

Characterization of Uncertainty in Modeling Scenarios:

There is a specific question regarding uncertainties that will address details, but little in the way of literature or other reference materials was evident to support the characterization of uncertainties with regard to the modeling setup itself, i.e., Model Uncertainty. According to the diagram and equations presented, a simple two-compartment model was put forward where emissions were solely in the first compartment- where the primary user was- and the an outer compartment, for which concentrations were affected by flow out of the inner compartment. The bystanders were located in the outer compartment. Questions were raised in the preliminary conference call regarding these scenarios- first by Dr. Driver, then by others. I do not think that the emissions rates and exchanges rates between compartments were well documented. In fact, they seemed more *ad hoc* than anything else. Can we get some more clarity on that via literature reference or, barring that, the reasoning behind the value choices?

In the inclusion of local exhaust ventilation (LEV), I think the models used make the untoward step of going from simple to simplistic. They make no real attempt to characterize the impact of LEV but rather they reference Wadden, Scheff, and Frank 1989. If memory serves me, Wadden, et al., make a more or less off-the-cuff statement that LEV can remove about 90% of airborne contamination when clearly many

factors are in operation for any given system. I do not believe that they ever intended this to be used in a quantitative sense. Many excellent scientists have spent their careers determining flow rates, capture efficiencies, and removal rates of LEV systems (See the works of, for example, Ellenbecker of UMass-Lowell, and Flynn of UNC.) Their application of this recommendation is also naïve; they simply reduce the emissions by a factor of 10. Such emissions would be markedly affected by the positioning of the LEV apparatus, the position of the degreaser/hobbyist in doing his/her work, capture efficiency of the LEV system, and the removal/exhaust of the captured air. If there is no removal or exhaust of the captured air, the LEV is completely ineffective. While this model may be used exclusively for scenario testing- and the scenarios themselves subject to great uncertainty in their utility- this just adds to the overall uncertainty of the risk estimates.

During our discussion on 17 July 2013, Dr. Jayjock brought forward a paper done by him and other co-workers evaluating the accuracy of the two-compartment model. The bottom line is that such a model produces concentrations that are likely no more than a factor of 3 different from measured values. This adds strong support to the use of the modeling system outlined for both decreasing facilities and hobbyists use, albeit less so for the latter. Yet no reference was brought forward for this paper by EPA, despite the fact that it would have strongly strengthened their case for using such a model to infer exposures.

The use of a steady-state assumption for concentrations is also problematic and perhaps simplistic for these scenarios. This is especially true of the hobbyist applications. As the name implies steady-state applications assume that all parameters in the model- emission rates, compartmental flow rates, sinks etc., are maintained for time periods “long” with respect to the characteristic time-scales of the overall system. If one is using TCE-containing materials in a semi-enclosed space it may take quite some time for steady-state to be established- perhaps longer than the scenario time, e.g., one hour, that is listed. Under such conditions, exposures maybe substantially different than those modeled for steady-state as the exponential approach to steady-state would afford lower concentrations than the steady-state values. Of course, one may argue that the models used here are screening tools and that estimates higher than what might be realistic are useful. If so, explicitly state this fact and indicate how large the impact of such might be on exposures, dose, and risks.

The industrial hygiene and indoor air literature is replete with papers dealing with these type of effects. It would appear that little effort was made to make the model more realistic in its applicability to the scenarios at hand.

While the above comments may appear to be excessively critical, they are given in the spirit of improving the transparency and readability of the document. EPA is to be commended for attacking a difficulty problem, especially in the case of the hobbyist exposure, for which few data are available to develop risk characterization. Nevertheless, EPA must address such issues and does best when taking on the problem as directly and clearly a possible. I stand ready to re-work my comments based on input from my colleagues, but these do represent my current thoughts. I look forward to further discussion at the full meeting.

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 the workplace exposure assessment, including estimations for bystander/non-users (e.g., women of childbearing age).

I have included many such comments under my response to Charge Question 1-2, and will not repeat those here. Instead, I will focus on improvements that might make the presentation clearer and more useful.

I advocate the use of sensitivity analysis of some type to ascertain the important parameters in the model used for worker exposure. While Dr. Jayjock's work suggests excellent accuracy for the two-compartment modeling system outlined in occupational applications, I believe that sensitivity analysis will aid in refining the model further. For the case of steady-state that might be approached in an industrial degreasing operation, there may still be some parameters of interest. For example, the ventilation rate for the room is fixed for this study. Concentrations, and thus exposures, are strongly (and almost linearly over narrow ranges) dependent on this parameter. This is true for both operator and bystander. Further, transfer rates from the source compartment to the "bystander" compartment strongly influence the concentrations experienced by both, and in the opposite sense, e.g., increased flow out of the source compartment lowers the exposure experienced by the source worker but increases the exposure experienced by the bystander. Since the risks shown at the end of the set of calculations are of interest if not for this group certainly for the home hobbyist, such an analysis is warranted.

Question 3-1: Please comment on the approach used and provide any specific suggestions or recommendations for alternative approaches, models, or information (e.g., information on duration and number of user events) that could be considered by the agency in developing the exposure assumptions and estimates for the hobbyist degreaser and clear protective coating spray uses, and for the bystander/non-users (e.g., children, women of childbearing age).

The approach used for the hobbyist scenarios suffers from many of the same shortcomings as the degreaser worker scenarios, but is likely more affected by parameter selection than is the industrial scenario. This is true because the exposures are intermittent and occur under much less controlled, and under poorly defined conditions. The hobbyist may well be a garage mechanic or other hobbyist with local ventilation determined by the garage opening, air "communication" from the house to the garage, open and closed windows, presence of sinks, and other variables poorly defined. Measurements on such systems are sparse for air contaminants in general and TCE contamination in particular. And, once again, these parameters strongly influence exposures.

It is important to note that the bystanders in this case are not other workers in a manufacturing facility but rather women of child-bearing age, young children, infants, and developing fetuses- a much more vulnerable population. Use of a limited number of scenarios for such a diverse population subject to exposure is not especially useful. Focusing, for example, on neurodevelopment, during specific stages of gestation and during infancy up to about age 18 months, similar exposures can produce substantially different neurodevelopmental effects ranging from mental retardation, behavioral problems, learning disabilities, and other potential problems. The simple scenarios and assumptions regarding movement of contaminants and exposure do not take into account specific, short-term life stages where neurodevelopment is critically affected by exposure.

Question 4-1: Please comment on the strengths and weaknesses of evaluating different endpoints based on exposure durations (i.e., acute versus chronic).

…and…

Question 4-2: Please comment on the strengths and weaknesses of using multiple values for each type of adverse effect.

These two topics is quite far removed from my area of expertise other than the neurodevelopmental work discussed above. However I can make a few general points.

For the degreaser worker, exposures are more or less uniform during the working day for both the operator and bystanders. This leads to a cleaner analysis for the chronic case. Acute exposures are less likely- spills, catastrophic events, etc., notwithstanding.

For the hobbyist, acute exposures are the principal operational effect. Indeed, exposures occur for a short duration and irregular intervals, although they are modeled as being more regular, e.g., 30 minutes every two weeks. Acute exposures are more difficult to assess both in terms of what the exposures would be as they are dependent upon conditions at the time, which may not afford a steady-state approximation, and what effects are likely to manifest given such exposures, as they are dependent upon life stage and other parameters.

In general, I think it incumbent upon EPA to look at different endpoints and multiple values for endpoint effects, e.g., AEGLs, to assess this problem.

Question 4-3: PBPK modeling was employed in the 2011 IRIS assessment for route-to-route extrapolation to develop a corresponding inhalation value from oral studies, some of which involved endpoints not studied or reported in inhalation studies. OPPT supports the approach used in the IRIS assessment. However, OPPT did not use PBPK-derived human-equivalent concentrations from oral studies in the current draft risk assessment, because OPPT focused on a narrow set of TCE consumer uses (e.g., degreasing and arts/crafts uses) that are subject to TSCA and therefore, OPPT's draft risk assessment relied only on inhalation exposure studies that directly mimicked inhalation exposure use scenarios for both adults and developmental lifestages. Please comment on whether the 2011 IRIS assessment's PBPK-derived inhalation values from oral studies should be used in the final OPPT risk assessment.

Again, this topic is outside my area of expertise. I only express concern for the large reliance on the 2011 IRIS assessment, as thorough as it was, for the final answer.

Question 5-1: Please comment on the strengths and weaknesses of the MOE approach used to estimate the chronic, non-cancer risk for the workplace exposures; including non- users.

…and…

Question 5-2: Please comment on the strengths and weaknesses of the MOE approach used to estimate the acute risk to consumers; including non-users (e.g., children, women of childbearing age). Specifically, please comment on the decision to limit the analysis to acute exposures without residual concern between events (i.e., once/week for users of the clear protective coating spray, and twice/month for degreaser users).

I will address both 5-1 and 5-2 together.

The calculations for Margin of Exposure (MOE) are outside my area of expertise. However, I have a few comments.

MOE calculations are relatively simple once the point of departure is determined. In this case, the point of departure is HEC99, which is very complicated to get at. It includes calculations of exposure and then from exposure the calculation of HEC99. In each case- depending on the direction one is going, one assumes a perfect calculation of the "other" number. For example, HEC99 assumes a perfect calculation of the exposure. Yet we have seen in our discussion that the exposure numbers obtained can vary

substantially due to uncertain conditions used to generate them. This uncertainty is not propagated through to the HEC99; exposure is assumed to be some fixed number. Conversely, if one were to be interested in calculating an exposure that would lead to a given HEC99, then that would be fixed and one would back-calculate the exposure assuming a fixed value. Yet we saw multiple HEC99s depending on endpoint and influenced by within- and between-individual variability and uncertainty.

This leads us to a full analysis of uncertainty in such models (See below). EPA has not presented an analysis of such even at the level of simple sensitivity analyses. The question of factors most strongly influencing the risk need to be addressed if not quantitatively, at least qualitatively in the text.

Question 5-3: Please comment on the use of a uniform benchmark MOE of 30 rather than a benchmark MOE equal to the composite Uncertainty Factors for each study as identified in the 2011 US EPA IRIS assessment for TCE.

The single, uniform MOE of 30 gives insufficient respect to the uncertainties of the various HEC99 values used for multiple endpoints. The quality of data for various HEC99 values differ as does the quality of exposure data for the various scenarios. For example, occupation exposures for the small-scale degreasing operations may be, as reported in Dr. Jayjock's paper, good to within a factor of 2-3 for both operator and bystander. Such is not likely to be the case for home hobbyist exposure. Further, calculation of HEC99 values based on these uncertain exposures themselves are not well calculated for various sensitive groups, e.g., pregnant women and young children. I should think that given such increased uncertainty for the sensitive populations that the MOE might be chosen differently- most likely larger- for these groups rather than relying on a single value.

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

I have really addressed this question throughout my comments. I do not think that the uncertainties in the estimates have been addressed well at all. The combination of data limitations on the exposure side, multiple outcomes on the risk side, and fixed methodology of the MOE calls the values chosen into question. One positive aspect of this analysis is that a very conservative, i.e., protective, point of departure- HEC99- has been used. However, we have no clear delineation of what this number really represents in terms of real-world exposure. It is likely to be quite protective, but is very uncertain. And because the results for certain outcomes are at levels of concern, it becomes incumbent upon EPA to set some limits on this uncertainty. Further, a sensitivity analysis may give direction for continued work in this area. Perhaps one or more parameters, e.g., HEC99, exposure, etc., maybe selected for further scrutiny based on its influence on risk uncertainty and/or lack of quality data.

Supplementary comments in response to EPA clarifying questions presented at August 21, 2013, TCE post-meeting

1. *Drs. Melnick and Ryan recommended that a sensitivity analysis be performed. Please provide specific suggestions on how the sensitivity analysis should be conducted. For instance, the agency performed a sensitivity analysis to characterize worst-case and typical exposure scenarios. This was done by varying parameters such as the room ventilation rate (from 500 cfm to 3000 cfm) and the effectiveness of local exhaust ventilation (from 0% to 95%); please provide the agency with alternative values for varying these parameters. Specifically, which other parameters should*

the agency vary and what values should be used? Where possible, please provide the supporting reference(s).

The process described here is not a sensitivity analysis but rather running a couple of different scenarios. A standard sensitivity analysis typically would vary each parameter or variable- generally one at a time- by a small amount, say 10% and evaluate the impact of that parameter on the model outcome. In the case of environmental concentrations, the variables may include emissions rates, application rates, volatility, etc. The impact of each is then rank-ordered and those giving the largest change in outcome are investigated further. It may be that some model variables have little effect on outcome over small ranges. Others may affect the outcome linearly or even super-linearly, e.g., a 20% change in outcome associated with a 10% change in input. Many modeling systems- even Crystal Ball- have such evaluations available as a single-step process.

As to what variables, the answer is simple- all of them. The algorithm is straightforward; increase the value of the given variable or parameter by some amount and observe the effect on the outcome of interest. Such procedures not only identify the sensitivity of the model to such perturbations, they also identify area where increased scrutiny of the variables and parameters might be warranted.

These questions are based on comments from Dr. Ryan:

1. *Please provide references containing available data relevant to sinks for TCE or chemicals comparable to TCE.*

A simple Google search “TCE sinks in indoor environments” yields a number of articles. The first to come up after the present work is a paper by An, Zhang, and Shaw published by the National Research Council of Canada entitled: “Sink Effect Study for Common Building Materials: A Literature Review and Research Plan.” Although published in 1997, this may be a good place to start. I also did a Web of Science Search using a similar criterion and recovered about 150 references. Inspection of the titles and abstracts led me to eliminate many of these. However 22 of these references are relevant to either one or the other of these questions or to questions on dermal exposure. They are given below. These include studies of TCE and other organic compounds in indoor environments modeling exercises, discussion of important factors influencing concentrations and exposure, and potential sources and sinks in residential environments.

2. *Please provide references for assessments that have varied parameters like compartmental flow or product composition with time, including currently available data that would permit such an analysis for TCE.*

See below:

Bogen, K. T., B. W. Colston and L. K. Machicao (1992). "Dermal Absorption of Dilute Aqueous Chloroform, Trichloroethylene, and Tetrachloroethylene in Hairless Guinea-Pigs." Fundamental and Applied Toxicology **18**(1): 30-39.

Borrazzo, J. E., C. I. Davidson and J. B. Andelman (1993). "Small Closed-Chamber Measurements for the Uptake of Trichloroethylene and Ethanol Vapor by Fibrous Surfaces." Modeling of Indoor Air Quality and Exposure **1205**: 25-41.

Candura, S. M. and E. M. Faustman (1991). "Trichloroethylene: toxicology and health hazards." G Ital Med Lav **13**(1-6): 17-25.

Chao, C. Y. and G. Y. Chan (2001). "Quantification of indoor VOCs in twenty mechanically ventilated buildings in Hong Kong." Atmospheric Environment **35**(34): 5895-5913.

Cornejo, J. J., F. G. Munoz, C. Y. Ma and A. J. Stewart (1999). "Studies on the decontamination of air by plants." Ecotoxicology **8**(4): 311-320.

Davis, W. T., C. C. Hood and M. Dever (1995). "Analysis of a Thin Activated Carbon Loaded Adsorption Medium." Separation Science and Technology **30**(7-9): 1309-1324.
Demou, E., S. Hellweg, M. P. Wilson, S. K. Hammond and T. E. McKone (2009). "Evaluating Indoor Exposure Modeling Alternatives for LCA: A Case Study in the Vehicle Repair Industry." Environmental Science & Technology **43**(15): 5804-5810.

Geng, C. N., Q. S. Luo, M. F. Chen, Z. Y. Li and C. B. Zhang (2010). "Quantitative Risk Assessment of Trichloroethylene for a Former Chemical Works in Shanghai, China." Human and Ecological Risk Assessment **16**(2): 429-443.

Heavner, D. L., W. T. Morgan and M. W. Ogden (1995). "Determination of Volatile Organic-Compounds and Ets Apportionment in 49 Homes." Environment International **21**(1): 3-21.

Hellweg, S., E. Demou, R. Bruzzi, A. Meijer, R. K. Rosenbaum, M. A. J. Huijbregts and T. E. McKone (2009). "Integrating Human Indoor Air Pollutant Exposure within Life Cycle Impact Assessment." Environmental Science & Technology **43**(6): 1670-1679.

Hughes, K., M. E. Meek and W. Windle (1994). "Trichloroethylene - Evaluation of Risks to Health from Environmental Exposure in Canada." Environmental Carcinogenesis & Ecotoxicology Reviews-Part C of Journal of Environmental Science and Health **12**(2): 527-543.

Lerner, J. E. C. and A. Porta (2011). "Study of air quality through passive diffusion samplers. Recovery of volatile organic compounds adsorbed." Afinidad **68**(556): 406-411.

Mendez-Roman, R. and N. Cardona-Martinez (1998). "Relationship between the formation of surface species and catalyst deactivation during the gas-phase photocatalytic oxidation of toluene." Catalysis Today **40**(4): 353-365.

Ohura, T., T. Amagai, Y. Senga and M. Fusaya (2006). "Organic air pollutants inside and outside residences in Shimizu, Japan: Levels, sources and risks." Science of the Total Environment **366**(2-3): 485-499.

Ondarts, M., C. Hort, V. Platel and S. Sochard (2010). "Indoor Air Purification by Compost Packed Biofilter." International Journal of Chemical Reactor Engineering **8**.

Pellizzari, E., P. Lioy, J. Quackenboss, R. Whitmore, A. Clayton, N. Freeman, J. Waldman, K. Thomas, C. Rodes and T. Wilcosky (1995). "Population-Based Exposure Measurements in Epa Region-5 - a Phase-I Field-Study in Support of the National Human Exposure Assessment Survey." Journal of Exposure Analysis and Environmental Epidemiology **5**(3): 327-358.

Sack, T. M., D. H. Steele, K. Hammerstrom and J. Remmers (1992). "A Survey of Household Products for Volatile Organic-Compounds." Atmospheric Environment Part a-General Topics **26**(6): 1063-1070.
Sexton, K., S. J. Mongin, J. L. Adgate, G. C. Pratt, G. Ramachandran, T. H. Stock and M. T. Morandi (2007). "Estimating volatile organic compound concentrations in selected microenvironments using time-activity and personal exposure data." Journal of Toxicology and Environmental Health-Part a-Current Issues **70**(5-6): 465-476.

Son, B., P. Breysse and W. Yang (2003). "Volatile organic compounds concentrations in residential indoor and outdoor and its personal exposure in Korea." Environment International **29**(1): 79-85.

Wu, C. and J. Schaum (2000). "Exposure assessment of trichloroethylene." Environmental Health Perspectives **108**: 359-363.

Yang, D. S., S. V. Pennisi, K. C. Son and S. J. Kays (2009). "Screening Indoor Plants for Volatile Organic Pollutant Removal Efficiency." Hortscience **44**(5): 1377-1381.

Calvin Willhite

General Comment

Assuming 1 hr domestic cleaning or 0.5 hr spray during arts and crafts activities with trichloroethylene (TCE), the OPPT presented the following daily indoor air TCE concentrations (Tables 3-11 and E-1):

- Solvent degreaser user (>16 years of age) 2.0 ppm (10.75 mg/m^3)
- Solvent non-user (>16 years of age) 6-8 ppm (32-43 mg/m^3)
- Clear protective coating user (> 16 years of age) 0.4 ppm (2.1 mg/m^3)
- Coating non-user (> 1 year of age) 0.1 ppm (0.54 mg/m^3)

The OPPT file Supplemental Information on E-FAST CEM Outputs (Degreaser Use) CEM Inhalation Exposure Estimates lists the following exposure concentrations for an assumed 1 hr use of TCE:

- Degreaser User (>16 years of age) peak concentration 48 ppm (259 mg/m^3)
- Non-User (21 years of age) peak concentration 7 ppm (38 mg/m^3)
- Degreaser User (21 years of age) lifetime average 0.11 ppm (0.66 mg/m^3)
- Non-User (21 years of age) lifetime average 0.04 ppm (0.21 mg/m^3)
- Degreaser user (16-20 years of age) lifetime average 0.009 ppm (0.05 mg/m^3)
- Degreaser non-user (16-20 years of age) lifetime average 0.004 ppm (0.0187 mg/m^3)

These values are said to equate to margins of exposure (MOE) of 2-8 for women of child-bearing age who use TCE degreasers and non-using females who live in the same home where hobbyist TCE activities occur. The OPPT considers these women at risk for adverse pregnancy outcome as a result of residential TCE use.

The US EPA (2013) already released its residential indoor air TCE concentration levels for both cancer (0.43 $\mu g/m^3$) and non-cancer (0.21 $\mu g/m^3$) endpoints. These US EPA (2013) residential indoor air concentrations are equivalent to a theoretical excess cancer risk of 1.0×10^{-6} and a hazard index (HI) of 0.1, respectively. Increasing the US EPA (2013) non-cancer residential indoor air concentration to 2.1 $\mu g/m^3$ equates to a HI of unity, somewhat less than the 18.7 $\mu g/m^3$ value calculated above. The cancer risk value is based on USEPA conclusions that occupational TCE exposure causes human kidney and possibly other cancers and the HI indicates that ingested or inhaled TCE poses an increased risk for cardiovascular malformations. Comparing the above 0.1-8.0 ppm results shows that all OPPT values (including non-user residents of homes) are substantially greater (not less than 900x) than the published US EPA (2013) residential indoor air *de minimus* risk TCE level; should the residential indoor air TCE value be increased to a HI of unity, the OPPT values are not less than ~100x the published US EPA (2013) residential indoor air TCE level.

For carcinogenesis, the US EPA adopted an inhalation potency factor (4.6×10^{-6} per mg/kg-day) based on human kidney cancer and an assumed mutagenic mechanism of action and released its residential air concentration (US EPA, 2013). Since the NRC (1993) has detailed methods for extrapolation of risks for long-term to short-term exposures for genotoxic carcinogens, why was it that method was not utilized to calculate the theoretical less than lifetime or short-term cancer risks associated with arts and crafts TCE exposure of concern to OPPT?

The non-cancer hazard index not only leads to calculation of the lowest equivalent 'safe' concentration of TCE in residential air, but those values are either less than or consistent with background TCE concentrations in United States urban or residential indoor air. As such, any domestic use of TCE in any amount for any use whatsoever will exceed the US EPA's published residential indoor air TCE level (0.21 $\mu g/m^3$). As written, the previously published and current US EPA reports lead to the conclusion that current ambient TCE levels are associated with increased risk for human cardiovascular malformations - yet there are no suggestions from studies of occupational TCE exposures at concentrations 1-2 magnitude of orders greater than ambient pose excess non-cancer health risks to those workers.

Given prior publication of US EPA (2013) guidance values for TCE in residential air, it is not clear why the current OPPT effort concerning domestic uses of TCE was deemed necessary? No empirical data are supplied and no literature reference was cited to support the assumed magnitude, frequency or duration of incidental TCE exposure during residential arts/crafts uses. While data for very high dose TCE-induced carcinogenesis in humans (Cherrie et al., 2001) can be considered convincing, fundamental biological problems with the OPPT non-cancer hazard indices and risk conclusions over concern for developmental toxicity render that aspect of the draft assessment unreliable. The draft document should be returned to the authors for major revision as there are substantial uncertainties in the domestic (hobby) exposure assessment and serious deficiencies in non-cancer hazard identification.

Specific Comment

Background

The document submitted for review relies upon previous USEPA analyses of health risks posed by environmental exposure to TCE (Chiu et al., 2013) that declared:

> "TCE is carcinogenic to humans by all routes of exposure and poses a potential health hazard for noncancer toxicity to the central nervous system, kidney, liver, immune system, male reproductive system and the developing embryo/fetus.
>
> Recent avian and in vitro mechanistic studies provided biological plausibility that TCE plays a role in developmental cardiac toxicity, the subject of substantial debate due to mixed results from epidemiologic and rodent studies."

Based on the results of the Chiu et al. (2013) health risk assessment taken together with TCE calculated exposure for residential degreaser and arts/crafts uses (0.8-2 ppm as a 24 hr mean airborne concentration), the OPPT concludes that non-cancer risk estimates for women of childbearing age during use of two hobbyist products indoors at home using developmental toxicity as the endpoint of concern yields a margin-of-exposure of 2 (Table 3-24). Based on the OPPT exposure assumptions and calculations, the Agency states use of TCE degreasers in the home (by either the female applicator or non-user woman in the home) presents an acute risk for developmental toxicity and also found: "In terms of acute effects, neurotoxicity seems less of a concern than developmental toxicity." Overall, the Agency concluded:

> "For the hobbyist degreaser user and non-user and for the hobbyist clear protective spray users, the acute non-cancer MOEs for developmental toxicity were less than 30 (potential risk concern)."

As conclusions on risk to human health are reflections of the intrinsic toxicity of TCE (e.g., 'hazard value') and the magnitude, frequency and duration of TCE exposure, the OPPT observed:

> "Thus, understanding that the exposure estimate may be an over- or under-estimation, the choice in the hazard value used will likely have a greater outcome of the risk assessment for the uses discussed in this document."

Charge to the Reviewer

Three key items formulated as Questions 1-1, 1-2 and 4-3 were requested of the present reviewer and these are addressed below. In order to place the answers to those questions into context, it is necessary to revisit the conclusions made by Chiu et al. (2013) and the data upon which those conclusions were based despite the specific charge to the OPPT review committee. Following that discussion, presentation of residential air concentrations associated with the Chiu et al. (2013) hazard value in relation to ambient and residential indoor air TCE concentrations are tabulated and conclusions on the wisdom of the Office of Chemical Safety and Pollution Prevention's (OPPT) document are offered. Those conclusions are followed by two recommendations that if implemented should increase the accuracy and credibility of the current assessment.

Question 1-1. Please comment on whether the characterization provides a clear and logical summary of EPA's analysis. Please provide specific suggestions for improving the document.

The answer to Question 1-1 has two components. The first concerns the assumptions and calculations of exposure estimates for small businesses and residential TCE uses. The second concerns the weight of evidence assessment used by and the conclusions reached by OPPT that environmental TCE exposure presents a serious risk for congenital heart malformations and increased intrauterine and neonatal death.

A. Exposure

The US EPA presents the results of calculations based on assumed quantities of TCE used during small business and home-based applications of the solvent in automotive parts cleaning and other recreational arts/crafts operations. No empirical area or personal monitoring data were collected to validate those exposure estimates; furthermore, there have apparently been no formal efforts to survey people who restore automobiles and other similar activities (e.g., home-based chain saw, lawnmower or other small engine service and repair) to ascertain duration and frequency of domestic TCE exposure. Most automobile hobbyists this reviewer queried at a local auto show did not use organic solvents at all, but instead due to cost and the inconvenience with recycling prefer detergent-based products. Of those who did respond in the affirmative, they soaked (rather than sprayed) their metal parts in (unidentified) solvents contained in a bucket with a tight lid (to retard evaporation and loss of liquid cleaner) for several hours or days and then only momentarily (and with rubber gloves) opened and closed their parts bucket. The purpose of the rubber gloves appears to be to avoid direct contact with oily organic solutions that defat the skin. Thus, this informal survey suggests a 1 hour per day exposure to uncontrolled TCE fume (perhaps by spray, cloth or brush application) is perhaps unlikely; the OPPT assumption appears to stem from shop practices used in the 1970s and 1980s and duration and the OPPT duration and frequency of exposure were determined by convenience ('expert judgment') without supporting empirical data.

At a minimum, the OPPT should expand Chapter 3 and Table 3-1 to include published indoor and occupational air TCE concentrations. The document should compare and contrast the results of the assumed exposure parameters and calculated lifetime average residential exposure concentrations with ambient levels of TCE in outdoor (0.1-18 ppb) (Bozzelli et al., 1980; Singh et al., 1982) and indoor

residential air where the US mean is 7.2 μg/m^3 (Shah and Singh, 1988) and with the TCE concentrations found in area and personal samples of workplace air. For example, the IRIS (2011) document tabulates the range of recent rural (0.005 – 1.9 μg/m^3) and urban (0.1 – 97 μg/m^3) ambient TCE concentrations and points to the mean personal 24 hr (breathing zone passive sampling) of Minneapolis residents (1.0 μg/m^3) (Sexton et al., 2005).

The magnitude of small business employee TCE exposure depends upon the nature of the operations and vapor controls (if any). A 1985 NIOSH survey of 23,225 industrial facilities where TCE was used found personal breathing zone concentrations of 1.2-5.1 ppm (6.7-27.3 mg/m^3) (Santodonato, 1985). Peak (15 min) exposures during industrial vapor degreasing can reach upwards of 200 ppm, but smaller (uncontrolled) benchtop TCE cleaning during repair of small metal components (as might occur in home automotive TCE use) occurred as 5-10 min events of 15 per day and 5 min events at 4 per day; those exposures rarely exceeded 10 to 15 ppm (Stewart et al., 1991). As to small business TCE exposures, perhaps the most recent robust data come from a 2010 study by the National Cancer Institute of 80 Chinese workers who used TCE in cleaning operations and their breathing zones were measured by full-shift personal sampling (22.19 ± 35.94 ppm) (Lan et al., 2010). Were the US EPA authors to query the NCI authors on the nature of those measurements and to survey small business operations it may be possible to place the exposure assumptions and resultant calculated levels into perspective in contrast to reliance upon assumed work practice.

B. Hazard Identification

Although the Agency stated it utilized a weight-of-evidence to conclude that environmental exposure to TCE "plays a role in developmental cardiac toxicity", in fact the Agency relied upon strength-of-evidence and selected the report by Johnson et al. 2003) to the exclusion of all other bioassays as the key study upon which its 2011 TCE Non-Cancer Reference Concentration (0.21 μg/m^3) is based. The current OPPT non-cancer risk conclusions are based on the same endpoint as those used to formulate the US EPA (2013) residential air guidance value. There is no evidence that NCEA applied a formal systematic method (e.g., Klimisch et al., 1997) to analysis of the published developmental toxicity studies with TCE; instead, the default hazard analysis and the most conservative BMDL01 (as contrast to the conventional BMDL10) treatment of the non-cancer toxicity data rests with the Johnson et al. (2003) drinking water study in rats. The Agency justified selection of the 1% risk (as contrast to the customary 10% value) as "due to the severity of defects, some of which could have been fatal", then applied a total toxicodynamic uncertainty factor of 10 resulting in an unusually low TCE Reference Dose.

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 characterization.

The information provided to substantiate the proposed hazard identification and potency for developmental toxicology of TCE has not been properly presented.

Chiu et al. (2013) point to TCE data in avian eggs to support their conclusion that TCE is teratogenic. There is no question that chick embryo data can show remarkable similarities with what has been seen in some rare instances with human beings and that chick embryo data can provide mechanistic insights for certain known human teratogens (e.g., Eichele et al., 1985; Lee and Tickle, 1985); however, chick embryo data alone are poor predictors of mammalian teratogens despite similarities in vertebrate morphogenesis. Concordance in response between species in teratology is the rare exception, rather than the rule. One of the fundamental difficulties with avian embryos in developmental toxicity is the inability to distinguish generalized toxicity from specific effects on development; increased concentrations of chemicals injected

into the egg increase embryonic death and the numbers of survivors may not at all reflect the teratogenic potential of the test material in mammals. In the case of TCE, the data cited by Chiu et al. (2013) have been extended to explore 8 and 800 µg/L injected into fertilized chicken eggs (Makawana et al., 2010; 2013) and the genomic data taken together with the stage-specific developmental data after injection of 0.4 to 400 µg/L (Drake et al., 2006) confirm vulnerability of the chick embryo when TCE exposure occurs during valvuloseptal morphogenesis.

Chiu et al. (2013) failed to qualify their conclusion that although no one species can uniformly predict human teratogens, the chick embryo is regarded by teratologists as a system that can only provide a basic but not definitive data for comparative toxicity. Haschek and Rousseaux (1997) summarized the experience as:

> "Although the chicken is useful in studying the progression of abnormal development, its relatively high sensitivity to exogenous agents and the significant differences in embryogenesis among avian and mammalian species preclude the use of chickens in standard teratogenicity testing."

Kimmel et al. (2009) [Attachment 1] described in detail some of the technical issues faced in determination of reasons for the discrepancies between the Johnson results and results in rodents from other laboratories. The US EPA would never accept submission of a non-guideline bioassay that has not been subject to the strict audit requirements of Good Laboratory Practices in support of regulatory decisions for new products submitted for registration, yet in the present case this is exactly what has occurred. While the Agency could require manufacturers and suppliers to submit the results of additional TCE developmental toxicity GLP bioassays in rodents and/or rabbits designed and conducted in accord with international test guidelines, it is unlikely this will resolve the fundamental scientific question whether TCE exposure (by any route or at any dose) presents a risk for human congenital cardiac defects as questions on the Johnson et al. (2003) and Collier et al. (2003) data remain.

Question 2-1. Please comment on the approach used and provide any specific recommendations for alternative approaches, models or information that should be considered by the Agency for improving the workplace assessment.

The Agency should cooperate with the Consumer Product Safety Commission and NIOSH to gather empirical TCE concentrations in area samples and personal breathing zone of people engaged in the activites involving TCE that are of concern to OPPT. Exposure assumptions and models are no substitute for empirical exposure data. At a minimum, the OPPT should solicit and welcome peer review of the current work product from NIOSH and the CPSC.

Question 3-1. Please comment on the approach used and provide any specific suggestions or recommendation for alternative approaches, models or information (e.g., information on duration and number of user events).

While the indoor air dispersion model used is common, it assumes solvent input from a constant source and justification of that constant source based on rare or intermittent hobbyist use of a TCE-containing aerosol spray can is needed. Since residential hobby exposures (e.g., automobile repair) ordinarily occur either outside (e.g., on the driveway) in good weather or likely in the garage during inclement weather, it is incumbent upon the authors to explain the exact conditions under which these activities are assumed to occur (e.g., in a two-car garage with the garage door open or closed, in a basement with little ventilation)

and provide the full range of TCE concentrations both in the operator's breathing zone as well in the immediate work area and then distributed throughout the other rooms of the residence taking into consideration single level and two story homes or apartments.
The Agency should cooperate with the CPSC and NIOSH to gather empirical TCE concentrations in area samples and personal breathing zone of people engaged in the activities involving TCE that are of concern to OPPT. Exposure assumptions and models are no substitute for empirical exposure data. At a minimum, the OPPT should solicit and welcome peer review of the current work product from NIOSH and the CPSC.

Question 4-1. Please comment on the strengths and weaknesses of evaluating different endpoints based on exposure duration.

While it is commendable to evaluate risk for different health endpoints and exposure durations, it is only the lowest value in practice that is important to the regulatory agency risk manager (often a civil engineer, an attorney and/or a political appointee). Assuming the carcinogenic potency of TCE is accurate, indoor air or workplace air TCE concentrations controlled so as not to exceed the risk range considered safe and protective of the public health (US EPA (*Federal Register* 56(20): 3526-3614, 1991) should also be protective for non-cancer health endpoints. Assuming the OPPT agrees with the IRIS conclusions on the human carcinogenicity of TCE exposure, it is not necessary to complicate risk communication to the project manager and to the public by presenting a menu of candidate values that are difficult to explain to an audience not familiar with exposure modeling, weight of evidence and statistical analyses when it is the highest potency and lowest exposure concentration that generally drive regulatory risk management.

Question 4-2. Please comment on the strengths and weaknesses of using multiple values for each type of adverse effect.

Ordinarily providing multiple oral Reference Doses or inhalation Reference Concentrations is useful since it provides the risk manager with a full range of candidate values, but in practice the risk manager generally selects only the lowest value. Generally the lowest values are associated with carcinogenicity and the theoretical risk range 10^{-6} to 10^{-4} as given by the USEPA (*Federal Register* 56(20): 3526-3614, 1991) in its statement that those risk values *are safe and protective of public health*. In the present case, of course, the lowest value is not related to carcinogenicity but to developmental toxicity.

During the July 9 presentation by OPPT of the draft health risk assessment for TCE the USEPA stated they relied not upon the Johnson et al. (2003) drinking water study where the cardiac defects were reported, but utilized the Healy et al. (1982) results. The ATSDR review of trichloroethylene concluded (page 43):

> "No statistically significant increases in skeletal, visceral or external malformations have been found in pups of rat dams exposed to 100-500 ppm of trichloroethylene." (Beliles et al., 1980; Hardin et al., 1981; Healy et al., 1982; Schwetz et al., 1975).

The ATSDR Toxicological Profile on Trichloroethylene (page 173) continued:

> "Following inhalation exposure, the effects noted at concentrations that were not overtly maternally toxic were decreased fetal body weight and incomplete ossification." (Dorfmueller et al., 1979; Healy et al., 1982).

Healy et al. (1982) allowed 32 pregnant Wistar rats to inhale 100 ppm TCE 4 hr/day on days 8-21 of gestation and compared the results with 31 control rats subject to the same conditions, but inhaled clear air. All of the rats were sacrificed on day 21 and the fetal hearts, ovaries, uterus, liver and lungs were dissected. There was no evidence of cardiac or other malformations in any of the offspring, but consistent with other publications found reduced fetal body weights and associated retarded skeletal ossification. Therefore, since "All studies investigating exposure to TCE vapors failed to detect any negative impact on the developing heart" (Watson et al., 2005) [Attachment 2], it is not accurate the OPPT took the position they used only the Healy et al. (1982) report since USEPA based the current assessment on increased risk for cardiovascular terata and no such effect was seen in the Healy et al. (1982) study.

For the current effort, it is not clear why USEPA selected Healy et al. (1982) as the key inhalation study for calculation of "safe" workplace and residential indoor air TCE concentrations? The Healy et al. (1982) protocol examined only a single 100 ppm concentration and, as such, there is no opportunity to evaluate concentration-response or determine a NOAEL or BMD. If in fact, the OPPT developmental toxicity risk estimate is based on the inhalation data, then why is it that the Careny et al. (2001) inhalation bioassay conducted in accord with OPPT's Guideline 870.3700 under Good Laboratory Practice was not utilized as the key study? In contrast to the Healy et al. (1982) protocol that examined only a single concentration, the guideline-compliant Carney et al. (2001) bioassay examined three concentrations (50, 150 and 600 ppm) and included dissection of fetal hearts and the great vessels. While there was some indication of maternal intoxication (reduced body weight gain) at the highest dose, there were no signs of treatment-related congenital defects (including cardiovascular malformations) at any concentration.

Question 4-3. PBPK modeling was employed in the 2011 IRIS assessment for route-to-route extrapolation to develop a corresponding inhalation value from oral studies, some of which involved endpoints not studied or reported in inhalation studies. OPPT supports the approach used in the IRIS assessment. However, OPPT did not use PBPK-derived human-equivalent concentrations from oral studies in the current draft risk assessment because OPPT focused on a narrow set of TCE consumer issues that are subject to TSCA and, therefore, OPPT's draft risk assessment relied only on inhalation exposure use scenarios for both adults and developmental lifestages. Please comment on whether the 2011 IRIS assessment's PBPK-derived inhalation values from oral studies should be used in the final OPPT risk assessment.

Physiologically-based pharmacokinetic models (PBPK) differ from classical multicompartment pharmacokinetic models that fit blood (the central compartment) data to concentration-time profiles for parent drug and metabolites to predict distribution and elimination rates and half-times to one or two peripheral compartments (of unstated anatomical location). Classical compartment models facilitate calculations of clearance as well as understanding dose-dependency (Inchinosa and Inchinosa, 2009). Contemporary PBPK models identify exact physiologic compartments and take into account species-dependent organ blood flows, tissue solubilities (e.g., partition coefficients), ventilation rates, parent compound uptake by different routes, metabolite generation and elimination (Leung, 2009). A rather large number of PBPK models have been developed for TCE and these were intended to address different endpoints ranging from neurotoxicity (e.g., Simmons et al., 2002) to carcinogenesis (e.g., Bogen, 1988). There is a long history in development of physiologically-based pharmacokinetic models for TCE in pregnancy beginning with the Fisher et al. (1999) effort. The current USEPA entry for TCE in IRIS system includes the following:

> "The estimates for kidney effects, thymus effect and developmental heart malformations are based on PBPK model estimates of internal dose for interspecies and intraspecies extrapolation and there is *sufficient* confidence

> in the PBPK model and support from mechanistic data for one of the dose metrics (total oxidative metabolism for the heart malformations)."

The IRIS (2011) evaluation developed candidate RfDs from oral studies as well as inhalation studies via route-to-route extrapolation using the "harmonized" PBPK model referenced in Chiu et al. (2013). The present PBPK work used the parameters listed in Table 3-18 and at page 56 the authors state: "This model was reviewed by the Science Advisory Board (US EPA, 2011a) and found to be *both useful and robust*." The present OPPT document provides neither clear rationale nor compelling reasons for deviation from the extensive US EPA PBPK-based interspecies scaling of rodent TCE data to human equivalent internal metabolized dose. Whether the lowest internal metabolized dose is associated with one or another route of exposure is actually of only minimal importance provided the PBPK scaling is robust and the results verified.

The suggestion that OPPT utilized only the Healy et al. (1982) inhalation developmental toxicity data is not accurate when in fact the OPPT relies upon the Johnson et al. (2003) rat drinking water data [Attachment 3] for its hazard identification of increased risk for cardiovascular malformations (see answer to Question 1-2 above). The suggestion that OPPT relied only upon the Healy et al. (1982) inhalation data is not consistent with how the data are used by other USEPA programs (USEPA, 2013). As the OPPT endorsed the IRIS data evaluations and no compelling reasons are offered to reject the Regional Screening Levels for TCE in indoor air of residences derived using conventional PBPK interspecies metabolized dose scaling in developmental toxicity (USEPA, 2013), the OPPT should (for sake of consistency with Agency-wide IRIS policy) utilize the identical endpoints and PBPK-based methods and assumptions as have been used to calculate the US EPA Regional Screening Levels (RSLs) for TCE in indoor air (USEPA, 2013).

Question 5-1. Please comment on the strengths and weaknesses of the MOE approach to estimate chronic noncancer risk for workplace exposures.

The question here concerns risk characterization. Published USEPA guidance (1989) calculates ambient and residential air concentrations based on threshold endpoints and presents those results as a Hazard Quotient ("The ratio of a single substance exposure level over a specified time period (e.g., subchronic) to a reference dose for that substance derived from a similar exposure period.") The noncancer Hazard Quotient is expressed as E/RfD where E= exposure level (or intake) and RfD = reference dose and E and RfD are expressed in the same units and represent the same exposure period. The Agency states:

> "The noncancer hazard quotient assumes that there is a level of exposure (i.e., RfD) below which it is unlikely for even sensitive populations to experience adverse health effects. If the exposure level (E) exceeds this threshold (i.e., if E/RfD exceeds unity), then there may be a concern for potential noncancer effects. As a rule, the greater the value of E/RfD above unity, the greater the level of concern."

Why it is the OPPT insisted on a MOE comparisons when the Hazard Quotient and Hazard Index methods are standard practice at federal and state agencies charged with environmental and consumer health protection? Does the OPPT advocate the Agency abandon the HQ and HI methodology in favor of a MOE approach?

Question 5-2. Please comment on the strengths and weaknesses of the MOE approach used to estimate the acute risk to consumers. Please comment on the decision to limit the analyses to acute exposures without residual concern between events.

The question here again concerns risk characterization. Published USEPA guidance (1989) calculates ambient and residential air concentrations based on threshold endpoints and presents those results presented as a Hazard Quotient ("The ratio of a single substance exposure level over a specified time period (e.g., subchronic) to a reference dose for that substance derived from a similar exposure period.") The noncancer Hazard Quotient is expressed as E/RfD where E= exposure level (or intake) and RfD = reference dose and E and RfD are expressed in the same units and represent the same exposure period. The Agency states:

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Why it is the OPPT insisted on a MOE comparisons when the Hazard Quotient and Hazard Index methods are standard practice at federal and state agencies charged with environmental and consumer health protection? Does the OPPT advocate the Agency abandon the HQ and HI methodology in favor of a MOE approach? If so, the document should explain why the MOE is a superior method compared to the standard HQ and HI methods.

Question 5-3. Please comment on the use of a uniform benchmark MOE of 30 rather than a benchmark MOE equal to the composite uncertainty factors for each study identified in the 2011 USEPA IRIS assessment for TCE.

As written, it is not clear why a MOE was used in the present OPPT analysis leading to beg the question which MOE is safe and protective of public health? If the OPPT rejects the non-cancer Hazard Quotient and instead adopts MOE comparison (as used in USEPA regulation of dietary pesticide residues), the application and rationale for the MOE approach and values used by the Agency in other regulatory actions should be referenced and the values used should be similar. If data or discrepancies are noted that dictate alternative MOE values, those should be articulated.

Question 5-4. Please comment on whether the document has adequately described the uncertainties and data limitations. Please comment on whether this information is presented in a transparent manner.

The general comments concerning the OPPT and IRIS conclusions on risk for cardiovascular malformations above illustrate the poor weight of evidence assessment carried out in this regard for TCE. The uncertainty attendant to the IRIS hazard identification for cardiovascular terata is so great that it leads to the present OPPT conclusion that all TCE exposures (including background concentrations in US urban ambient and indoor residential air) present increased risk for congenital malformation of the heart and great vessels.

It is not clear why OPPT relied on the results of the Johnson et al. (2003) study to the exclusion of all other inhalation and oral developmental toxicity studies in rodents and rabbits. If in fact the OPPT is reliant upon only the inhalation data, why is it the Carney et al. (2001), the Schwetz et al. (1975), the Hardin et al. (1981), the Beliles et al. (1980) or the Dorfmueller et al. (1979) study was not used? Why is there no discussion of all of the available developmental toxicity inhalation bioassays in the present analysis?

Since there are no empirical indoor air TCE concentration measures for either the small shop or residential use of spray cleaners that contain TCE and the assessment relies upon model estimates including assumptions on duration and frequency of these operations that have not been validated, confidence in the accuracy of the results of the OPPT assessment is called into question.

Summary

As submitted, the exposure parameters appear arbitrary (e.g., 0.5 and 1 hr/day) and may have been selected for sake of convenience. The data upon which conclusions put forward by OPPT on risk for developmental toxicity associated with arts and crafts use of TCE are not reliable. Nearly all developmental toxicity studies with TCE in rodents find no sign of teratogenicity (e.g., Beliles et al., 1980) or find only slight developmental delay (Dormueller et al., 1979). Chiu et al. (2013) cite the NRC (2006) report as verification of their risk assessment for TCE developmental toxicity, but actually the NRC (2006) concluded:

> "Additional studies evaluating the lowest-observed-adverse-effect-level and mode of action for TCE-induced developmental effects are needed to determine the most appropriate species for human modeling."

In its present assessment, the OPPT ignored the serious deficiencies already identified in conduct of the Johnson et al. (2003) rat drinking water study upon which the BMD01 was based (Kimmel et al., 2009; Watson et al., 2006) [Attachments 1 and 2]. In their weight-of-evidence assessment, Watson et al. (2006) concluded:

> "…application of Hill's causality guidelines to the collective body of data revealed no indication of a causal link between gestational TCE exposure at environmentally relevant concentrations and congenital heart defects."

Those conclusions were consistent with Hardin et al. (2005). Perhaps most disturbing of all in US EPA's reliance upon Johnson et al. (2003) as the key study (which for the basis for their lowest non-cancer TCE hazard index and margin of exposure) is the observation by Hardin and associates (2004):

> "Conventional developmental and reproductive toxicology assays in mice, rats and rabbits consistently fail to find adverse effects of TCE on fertility or embryonic development aside from embryo- or fetotoxicity associated with maternal toxicity. Johnson and Dawson, with their collaborators, are alone in reporting that TCE is a "specific" cardiac teratogen."

One of the fundamental tenants in science is the reliability and reproducibility of results of scientific investigations. In this regard, one of the most damning of the TCE developmental toxicity studies in rats is that by Fisher et al. (2005) who stated:

> "The objective of this study was to orally treat pregnant CDR(CD) Sprague-Dawley rats with large bolus doses of either TCE (500 mg/kg), TCA (300 mg/kg) or DCA (300 mg/kg) once per day on days 6 through 15 of gestation to determine the effectiveness of these materials to induce cardiac defects in the fetus. All-trans-retinoic acid (RA) dissolved in soybean oil was used as a positive control.
>
> The heart malformation incidence for fetuses in the TCE-, TCA- and DCA-treated dams did not differ from control values on a per fetus or per litter basis. The RA treatment group was significantly higher with 33% of the fetuses displaying heart defects."

Unfortunately, Johnson et al. (2005) failed to report the source or age of their animals, their husbandry or provide comprehensive historical control data for spontaneous cardiovascular malformations in their colony. The Johnson study with 55 control litters compared to 4 affected litters of 9 treated was apparently conducted over a prolonged period of time (perhaps years); it is possible this was due to the time required to dissect and inspect fresh rodent fetuses by a small academic research group. However, rodent background rates for malformations, anomalies and variants show temporal fluctuations (WHO, 1984) and it is not clear whether the changes reported by Johnson et al. (2005) were due to those fluctuations or to other factors. Surveys of spontaneous rates of terata in rats and other laboratory animals are common particularly in pharmaceutical and contract laboratory safety assessment (e.g., Fritz et al., 1978; Grauwiler, 1969; Palmer, 1972; Perraud, 1976). The World Health Organization (1984) advised:

> "Control values should be collected and permanently recorded. They provide qualitative assurance of the nature of spontaneous malformations that occur in control populations. Such records also monitor the ability of the investigator to detect various subtle structural changes that occur in a variety of organ systems."

Rates of spontaneous congenital defects in rodents can vary with temperature and housing conditions. For example, depending on the laboratory levocardia and cardiac hypertrophy occur in rats at background rates between 0.8-1.25% (Perraud, 1976). Laboratory conditions can also influence study outcome; for instance, maternal hyperthermia (as a result of ambient elevated temperature or infection) can induce congenital defects (including cardiovascular malformations) in rodents and it acts synergistically with other agents (Aoyama et al., 2002; Edwards, 1986; Zinskin and Morrissey, 2011). Thus while the anatomical observations made by Johnson et al. (2003) may be accurate, in the absence of data on maternal well-being (including body weight gain), study details (including investigator blind evaluations), laboratory conditions, positive controls and historical rates of cardiac terata in the colony it is not possible to discern the reason(s) for the unconventional protocol, the odd dose-response and marked differences between the Johnson et al. (2003) results and those of other groups.

As noted by previous investigators, the rat fetus is "clearly at risk both to parent TCE and its TCA metabolite" given sufficiently high prenatal TCE exposures that can induce neurobehavioral deficits (Fisher et al., 1999; Taylor et al., 1985), but to focus on cardiac terata limited to studies in one laboratory that have not been reproduced in other (higher dose) studies and apply the BMD01 with additional default toxicodynamic uncertainty factors appears misleading.

There was some suggestion during the July 9 USEPA oral presentation of the TCE arts and crafts risk assessment that data from Forand et al. (2012) may be taken as support for the very low developmental toxicity margin of exposure (2) presented in the OPPT assessment. Forand et al. (2012) concluded:

> "The study's strongest finding is for an association of
> TCE and PCE exposures with cardiac birth defects…"
> (specifically conotruncal cardiac malformations).

This association was seen with a median Endicott, New York, indoor ambient TCE concentration of 16 $\mu g/m^3$ (a value 8x greater than the US EPA 2013 residential indoor air RSL and equivalent to the current proposed OPPT lifetime average TCE concentration of 18.7 $\mu g/m^3$ for excess non-cancer risk for the 16-20 year old residential non-user of TCE products). Forand et al. (2012) made an effort to account for tobacco use by their mothers, but admitted, "…the inability to control for smoking is also an important limitation in this study." Forand et al. (2012) did qualify their association and noted the wide confidence intervals on relative risk.

Unfortunately, congenital heart disease is the single most common birth defect affecting ~1% (some 40,000) of all live births each year in the United States. While an apparent association between indoor air TCE and adverse pregnancy outcome could be interpreted in some circles, the Forand et al. (2012) study has a number of important deficiencies. While Forand et al. (2012) did attempt to account for smoking, their protocol failed to account for common known risk factors for cardiovascular terata. Maternal obesity increases risk for atrial septal defects, pulmonary stenosis, tetraology of Fallot, aortic stenosis and hypoplastic left heart (Mills et al., 2010), maternal diabetes mellitus presents a 5x increase risk for transposition of the great vessels, persistent truncus arteriosus, triscupid atresia and single ventricle (Wren et al., 2003; Lipowski et al., 2010; Fahed et al., 2013), maternal alcohol consumption increases atrioventricular septal and other defects (Burd et al., 2007; Smith et al., 1981), maternal disease (rubella, lupus) and inherited conditions including Down's syndrome that increase the incidence of aberrant subclavian artery, patent ductus arteriosus, atrioventricular septal defect and tetralogy of Fallot (Chang et al., 2013; Fahed et al., 2013; Gelb, 2000; Lo et al., 1989; Stallmeyer et al., 2010) were not included. Moreover, Forand et al. (2012) made no effort to determine whether the mothers in their study used any of the common pharmaceuticals known to cause human cardiovascular malformations including those used to control epilepsy (Samrén et al., 1997), to treat dermatologic conditions (Lammer et al., 1985), to treat depression (Källén and Olausson, 2006; Bérard et al., 2007; Oberlander et al., 2008) or whether they were afflicted with maternal conditions like phenylketonuria or had reduced folate, protein deficiency or used dietary supplements (Yano et al., 2013) that increase risk for cardiovascular terata.

Therefore, prior to any suggestion the Forand et al. (2012) observations be entered into a developmental toxicity weight-of-evidence for TCE exposure and risk of cardiovascular terata, the Forand et al. (2012) study should be subjected to independent critical review by epidemiologists and experts in teratology who have experience with these types of studies.

Conclusion

These sorts of situations in toxicology are neither novel nor new and history demonstrates mistakes by the US government in chemical hazard identification. Two brief examples illustrate the problem. For many years the US EPA considered the solvent 1,1,-dichloroethylene (also known as 1,1,-DCE or vinylidene chloride) to be a probable human carcinogen, a conclusion based on rat data reported by a single laboratory in spite of the fact 16 other cancer bioassays found no such effect. The 1,1-DCE cancer risk assessment was ultimately withdrawn by USEPA after many years of contentious debate. A second example concerns the US Consumer Product Safety Commission that concluded certain hobby spray

adhesives were responsible for human birth defects and instituted a nationwide ban. This ban was subsequently withdrawn after the data upon which the action was based were found without merit - but retraction of that CPSC regulatory activity occurred only after concerned mothers elected to abort their pregnancies (Hook and Healy, 1976).

Taking at face value the lifetime mean concentrations calculated by OPPT for the present exercise, this reader comes to the conclusion that sexually active fertile women of child-bearing age who live in homes with the mean US indoor air TCE concentration (7.37 $\mu g/m^3$) are at increased risk of adverse pregnancy outcome. As written, the OPPT analysis leads one to the conclusion that to exposure to "background" urban ambient and/or indoor air concentrations of TCE presents increased risk for cardiac malformations whether or not the mothers themselves use TCE or live in a home where TCE is utilized during arts and crafts activities.

Recommendations

The debate over TCE non-cancer hazard identification and potential risk of congenital malformations illustrates the difficulty in identification of human teratogens based on avian and rodent data. There are at least two pathways forward to resolution of this problem.

First, historical concentrations of TCE in US workplace air averaged 38.2 ppm (210 mg/m^3) (with the highest levels 44.6 ppm during vapor degreasing) across all industries (Bakke et al., 2007). While TCE consumption has declined since the 1970s when some 200,000 US workers (many of whom were females employed in dry cleaning) were exposed (NIOSH, 1973) or in the 1990s when ATSDR (1997) tabulated US facility air emissions (ATSDR Table 5-1) wherein daily occupational exposures amounted to 0.03-13.6 mg/kg-day, there are hundreds of facilities that use TCE to this very day. The OPPT estimates 7,415 employees currently work in small commercial degreasing operations in the US and that they experience 8 hr TWA exposures of 2-6 ppm. In addition, the OPPT estimates that there are up to 17,796 (far field) workers exposed at 8 hr TWA values between 1-5 ppm with worst-case concentrations on the order of 17-63 and 9-55 ppm (Tables 3-8, D-2 and D-3). It is not clear why either retrospective or preferably prospective epidemiologic pregnancy outcome data (adjusting for maternal age, parity, folate status, tobacco and alcohol use, exposures to known human cardiac teratogens and socioeconomic status) have not been collected from state (e.g., California Birth Defects Monitoring Program) and private (e.g., Kaiser Permanente) birth defects registries? If this is because no suitable US data are available, why has the US EPA in collaboration with other federal agencies not evaluated pregnancy outcome data for offshore TCE exposures as was done by Lan et al. (2010) in their evaluation of TCE immunotoxicity? A number of publications that describe robust studies of benzene exposure among Chinese occupational cohorts have been valuable in assessment of the shape of the benzene concentration-response relationship; it is not clear why similar studies could not be conducted with TCE to investigate reproductive failure? The reliance upon community-based (ecological) TCE studies with unreliable or no empirical exposure data in relation to pregnancy outcome is feeble.

Second, the current TCE debate in developmental toxicity has historical parallels with the debate over the teratogenic activity of selenium (Se) and steps taken to resolve that matter. Selenium is an unequivocal teratogen in wild birds (Hoffman et al., 1988; Hoffman, 2002), injection of Se into chicken eggs causes cardiac malformations (Khan and Gilani, 1980) and mechanistic data implicate lipid peroxidation in the pathogenesis of Se-induced cardiac terata in avian species (Padmaja et al., 1993). Not only are there case reports of Se-associated congenital defects in humans, but consumption of high Se diets by ruminants and high doses of Se in hamsters can be teratogenic. Overall, the results in rodent studies with Se found reductions in the numbers of live births, increased fetal death and decreased fetal and pup body weights, but no such effects were seen in controlled dietary studies with pigs (reviewed in ATSDR, 2003). In order

to address the uncertainty over the potential developmental toxicity of ingested Se, controlled oral intubation studies in pregnant non-human primates were conducted at doses up to maternally maximum tolerated doses together with collection of maternal, transplacental and neonatal kinetic and disposition data (Tarantal et al., 1991; Hawkes et al., 1994). The advantage to the non-human primate, of course, is their comparatively large size and similar anatomy, physiology and general metabolic handling of xenobiotics. Those studies found that after repeated daily ingestion of up to near lethal doses of the most highly bioavailable dietary Se form during organogenesis there was no evidence whatsoever for manifestations of developmental toxicity. The debate over the potential developmental toxicity of ingested Se following publication of those reports ceased.

Therefore, adoption of the 2011 US EPA hazard identification for TCE as a suspect or potential human teratogen is not supported by the weight of evidence of all of the available data (Hardin et al, 2005; Watson et al, 2006). This situation can be addressed either by study of pregnancy outcome among women currently employed in US or offshore industries who are exposed to much higher TCE levels in air than the OPPT considers represent increased teratogenic risk or by controlled study of TCE kinetics and pregnancy outcome in non-human primates.

See 'TCE_Post July 17_Willhite Attachments_3 of 3_FINAL.docx' for additional material from Dr. Willhite.

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Calvin Willhite (Attachment 1)

Project: 0904539.000

Comments on the EPA Toxicological Review of TCE: Developmental Effects

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The evidence used by the EPA to support the claim that TCE and/or its metabolites are specific cardiac teratogens comes from both human epidemiology investigations and studies in experimental animals. In both cases, the arguments are not persuasive of a causal linkage. Not only does the cited epidemiology literature fail to satisfy the Hill criteria for causation, it also fails to link the purported findings to TCE exposure. In addition, the EPA assessment is incomplete insofar as it does not consider the most recent and comprehensive animal studies (see below) regarding the effects of TCE and its major metabolites in pregnant mammals. The literature cited to support the contention that TCE and/or one of its metabolites is a cardiac teratogen is over interpreted.

The Cited Human Data Do Not Support a Causal Association between TCE Exposure and Birth Defects

The studies that allegedly support the contention that TCE exposure of pregnant women resulted in births of infants with cardiac or other developmental defects find significance by combining many types of malformations into large categories that sound related, but are not. For example, the category of "cardiac malformations" is used loosely to include alterations in the structure of the heart as well as alterations in the arrangement of the large blood vessels. Not only are the subject organs different, but also they have very dissimilar embryological development.

The human epidemiology studies used to support this contention are of two general types. The first includes investigations of births from regions that had contaminated water supplies. Goldberg et al. (1990) investigated births in a region of Arizona that had an aquifer contaminated with 6 – 239 ppb TCE. The authors reported the incidence for 33 types of malformation associated with the cardiovascular system, among which were 12 diagnoses that were predominantly malformations of the great vessels, such as transposition of the great vessels, coarctation of the aorta, interrupted aortic arch, and patent ductus arteriosus. A total of 44 non-cardiac malformation cases (18% of the total cases) was reported. What is remarkable about these studies is the low exposure concentrations of TCE. As will be discussed below, those animal studies that did report positive results had lowest observed effect levels (LOELs) that were four to six orders of magnitude higher than the highest reported contamination level in the Arizona aquifer.

The "cardiac anomalies" reported in the contaminated Arizona aquifer studies contrast with the results of other epidemiology studies. For instance, Wilson et al. (1998) examined data from the Baltimore-Washington Infant Study and concluded that "solvents/degreasing agent exposure" (inclusive of TCE and many other substances) accounts for 4.6% of the attributable risk for hypoplastic left heart syndrome, but no attributable risk for anomalies including transposition of the great vessels and coarctation of the aorta. The findings in this study contrast with those of the Goldberg study mentioned above, where the individual malformations that together comprise hypoplastic left heart syndrome (aortic valve stenosis, mitral stenosis, hypoplastic left ventricle) accounted for only 15 cases (6% of the cases reported). Thus, there is poor concordance between these two study populations (i.e., three-fold difference in rate of occurrence and different types of "cardiac anomalies").

A study of births in 75 towns of New Jersey that experienced water supply contamination by a variety of agents, including TCE at an average of 55 ppb, reported significant associations between TCE contamination and "cardiac defects" and neural tube defects (Bove et al., 1995). Once again these categories were very broad and included multiple anomalies with very different modes of formation. It is peculiar that the reference population of >55,000 births in this study was stated to have experienced no birth defects. This is an incredible statement, because the background rate of major malformation in the United States is 1 – 3% (550 – 1650 expected cases in a population of 55,000), and neural tube defects and heart defects are among the most common, having an overall expected incidence of ~100/10,000

(DeSesso et al., 1999; Hoffman and Kaplan, 2002). The authors reported as significant those effects that occurred with an odds ratio of 1.5 or greater, but they used relaxed 90% confidence intervals. In the case of the TCE-exposed population, for instance, the incidence of neural tube defects was reported as 56/81,532 or 6.9/10,000, which is well within the expected number of cases based on the national incidence rate, although it is obviously higher than the "0" seen in the reference population. Notably, hypoplastic left heart syndrome (normal rate of occurrence ~2/10,000 births) was not associated with TCE contamination (see discussion below).

A shortcoming that is common to all of the epidemiology studies is the lack of accurate exposure information and poor control of confounding factors. In the instance of the Arizona aquifer, the authors were clear to point out that their data showed "a significant association but not a cause and effect relation between parental exposure to the contaminated water area" and cardiac defects. By this they meant that the parents of affected children were present in the land area overlying the aquifer during early gestation– but not that they had necessarily drunk or used contaminated water. Thus, exposure was not quantified. With respect to the Baltimore-Washington Infant Study, interviews with parents identified activities and occupations that were likely to have involved organic solvents and degreasing substances. TCE is among the substances that could have been used, but it was not singled out as a causative agent and there is no information on levels of exposure. These data-sets fail to clearly identify a specific causative agent and do not quantify exposure levels, making the assessment of risk for a particular chemical (e.g., TCE) unfeasible.

As detailed above, the human data cited by the assessment are inadequate for risk assessment. In the absence of clear-cut human data, strong evidence from animal studies in addition to good mechanistic information can help in the assessment of risk.

Data from Early Animal Studies Have Been Used Without Critical Evaluation

Papers from the EPA laboratories in Cincinnati (Smith et al., 1989, 1992; Epstein et al., 1992) first reported cardiovascular anomalies in fetal rats whose mothers had received doses of the TCE metabolites TCA (up to 1,800 mg/kg/day) or DCA (up to 2,400 mg/kg/day) by gastric intubation during gestational days 6 – 15. The spectrum of cardiac malformations observed in these studies was unique. They included many cases of "levocardia" (displacement of the heart towards the left side of the thorax) and a defect that appears to have been very high in the membranous portion of the interventricular septum (the wall that separates the left and right ventricles and participates in the separation of the aorta from the right ventricle). As will be detailed later, other laboratories have not reproduced these malformations.

The question arises as to the cause of the observations in these first studies. It should be noted that the doses used in these studies were six to seven orders of magnitude higher than the dose expected for a 65-kg pregnant woman who drinks water containing TCE at the concentration resulting from application of the proposed reference dose (RfD)(13µg/L). Further, the pregnant rats in the groups with anomalous fetal hearts experienced severe maternal toxicity, evidenced by diminished body weights at study termination, decreased weight gains during gestation, and total litter resorptions. The offspring from the affected litters had mean fetal weights that were approximately 33% lower than control values, as well as concomitant decreases in fetal size (e.g., decreased crown-rump lengths). In rats, the last 48 hours of gestation are a period of rapid growth; not only do the fetuses gain much weight in this period, but also the thorax grows quickly to accommodate the lungs, which develop largely after birth (Rakusan, 1984; Burri et al., 1974). While it is possible to associate the cardiac effects with the aforementioned maternal and fetal toxicities, there may be another contributing factor. Some findings in developmental toxicity studies can be caused by too over-zealous dissection methods (Harris and DeSesso, 1994). Fresh dissection of rat fetuses for examination of thoracic contents and dissection of the heart to observe internal cardiac structure is a demanding procedure because of the small size of fetuses. In fetuses that are one-third smaller than normal, the effort is even more difficult. The delicate tissues of compromised

heart (especially the diaphanous tissue of the membranous interventricular septum) can be easily disrupted during the incision and opening of the heart.

In a subsequent paper that laid out a proposed general toxicity-neurotoxicity-developmental toxicity screening approach, Narotsky and Kavlock (1995) administered large doses of TCE (1,125 or 1,500 mg/kg/day) by gastric intubation to pregnant Fisher 344 rats on gestational days 6 – 19 and allowed the animals to deliver their litters. The maternal animals experienced noticeable toxicity at both doses. Pup weights were significantly decreased in both treated groups, and the pups were reported to have experienced "increased incidences of micro/anophthalmia," although the numbers associated with these lesions were not reported. In the absence of data it is not possible to independently evaluate the latter conclusion. The thoracic contents (including hearts) were not examined. One notable design characteristic is the exaggerated dose of the material relative to the expected human exposure levels, as noted for the preceding studies. This brings into question the relevance of these findings for risk assessment purposes.

In 1998, Johnson et al. studied a variety of TCE metabolites for potential effects on cardiac development in pregnant Sprague-Dawley rats by providing drinking water that contained one of the TCE metabolites (including TCA, MCA [monochloroacetic acid], DCVC, and others) from gestational day 1 throughout pregnancy. They reported an increased incidence of cardiac anomalies only in pups from the eleven rats that had received water that contained 2,730 ppm of TCA. The defects included four cases of defects in the membranous interventricular septum. These findings are provocative, given the early reports by Smith and colleagues, but are in need of verification because of the small number of maternal animals in the TCA group, the lack of a dose-response design, and the low number of cases. As discussed in the next section, a robust follow-up study has been completed and was unable to reproduce the findings.

In addition to the whole animal studies mentioned above, the EPA assessment reviews data from papers that have designs that are inappropriate for risk assessment. The papers include those of Dawson et al. (1990) wherein solutions of TCE (15 or 1,500 ppm in saline) were delivered directly to the uterine lumina of pregnant Sprague-Dawley rats by osmotic mini-pumps that had been surgically implanted in the abdominal cavities on gestational day 7. While alterations were observed in several fetuses, there were no cases of ventricular septal defects. Administration of compounds by such an irrelevant route provides little information about the potential risk due to environmental or occupational exposure to TCE. The other paper that deserves mention is that of Boyer et al. (2000) who explanted the atrioventricular canals from stage 16 chick embryos and cultured them in a collagen gel that contained 0 - 250 ppm TCE. The authors noted that mesenchymal cell formation was inhibited in cultures containing TCE. The findings of this study are not relevant to human health risk assessment for a variety of reasons. First, avian developmental models differ significantly from mammalian models due to the absence of a maternal influence and a placenta. Second, the dose at the exposed tissues in the culture system is static and is likely to be far higher than the target tissue dose in developing mammalian hearts. Third, the culture method is not widely used and there is little background data with which to compare the results of the experiments.

Review of Johnson et al. (2003) Paper (Critical Study) and Associated Studies.

The fact that Johnson et al. (2003) is actually a compilation of data from two or more studies, the first published ten years before the 2003 publication (Dawson et al., 1993), was not made clear in their paper. In fact, it appears that it took a letter to the editor (Hardin et al., 2004) to have the authors explain this situation (Johnson et al., 2004). This gives the appearance that the authors were unaware of how to design studies, analyze and present developmental toxicity data.

There are a number of concerns regarding these studies:

First, it is not clear where all of the data reported in Johnson et al. (2003) came from. Currently, we are aware of two papers: Johnson et al. (2003) and Dawson et al. (1993). These are the two papers that are referenced in their response to Hardin et al. (2004), but, there is no indication in the summary paper (Johnson et al., 2003) of which data came from Dawson et al. (1993) and which data came from later studies.

Johnson et al. (2003) do not provide data on maternal and fetal parameters other than cardiac malformations, only mentioning that "maternal and fetal variables, including noncardiac congenital abnormalities, showed no significant differences between treated and control groups." Dawson et al. (1993) did not provide any control data for maternal and fetal parameters, other than cardiac abnormalities. Consequently, there is no way to assess the impact of exposure on any parameter other than cardiac abnormalities, including such parameters as maternal body weight and body weight gain, fetal weight, and fetal viability. Johnson et al. (2004) note in their editorial reply that "Control values were consistent throughout our studies," however, there is no way for the reader to determine that.

Dawson et al. (1993) do not mention the number of pregnant dams that were assigned to each treatment group. There is no way to determine how much of the data in Johnson et al. (2003) is from the Dawson et al. (1993) study.

It would be prudent to have a qualified statistician look at this data base and the statistical evaluations used. Given the pooling of discrete data and the unbalanced study design (55 dams in the control vs. 9-13 in the treatment groups), it would be interesting to know how a statistician would view the analysis. Moreover, can the analysis address the hypothesis? Johnson et al. (2003) indicate that their goal was to determine whether there was a threshold level of TCE in drinking water above which the incidence of congenital cardiac defects in the rodent increased significantly. Does their study design and statistical analysis permit the testing of a hypothesis derived from this goal? They do report that their data could indicate that a threshold effect exists at a level between 1.5 and 1,100 ppm. That is a range of three orders of magnitude, which is not very useful in establishing reference concentrations.

In discussing the dose-response pattern in these studies, Johnson et al. (2003) specifically comment on the response of the highest exposure (1,100,000 ppb) relative to control, but they only mention that "Intermediate exposure levels produced intermediate response rates." While this is true, the intermediate levels did not produce a clear dose-response relationship. The 2.5 ppb exposure level did not show any effects, even though 16.4% of the control litters had a cardiac defect. Moreover, there was a reduced (or at best an equivalent) response between 250 ppb and 1500 ppb. Johnson et al. (2003) provide a rationale for choosing the exposure levels that were used, but the extreme range makes it difficult to examine whether a continuous response pattern exists. To make the analysis more difficult to interpret, the fetus and not the dam (litter) was used as the experimental unit, or at least was the unit where statistically significant responses were noted. The dose-response pattern may be another area where the input of a qualified statistician/modeler would be prudent.

Johnson et al. (2003) comment that TCE exposure using an in vitro chick model has been shown to have effects on several elements of epithelial–mesenchymal cell transformation at concentration ranges that correlate with their findings. They note a concentration range of 50-250 ppm (although it isn't clear if this is the only concentration range used in the referenced studies). If the 50-250 ppm is correct, it does not correlate with the Johnson et al. (2003) concentration range. It is bounded by the Johnson et al. concentration range, but then, almost any range would be, given the extreme range that Johnson et al. used. More importantly, an application of any concentration of TCE in an in vitro chick embryo study is in no way comparable to an application of any other concentration of TCE in drinking water in an in vivo

rat study. It is unclear why the authors even make this statement; are they suggesting that their drinking water dose range would produce similar inhibitions of the transcription factors?

Johnson et al. (2003) do not reference Fisher et al. (2001), even though Johnson was one of the authors of the latter study and part of the cardiac examination team. Fisher et al. (2001), using techniques similar[1] to those reported in Johnson et al. (2003), did not find any cardiac defects following exposure to 500 mg/kg/day TCE. They provide some possible explanations for the differences from the Dawson et al. (1993) study: TCE purity, rat strains (both used Sprague-Dawley, different sources?), and experimental design (see above footnote), and the use of a staining procedure in the Fisher study "to better visualize heart structure." This last comment is surprising, since if the hearts were better visualized, one would expect that more, not zero, affected hearts would have been found.

One additional note: In their conclusions, Fisher et al. (2001) comment:

> "The high background of fetal heart malformations on a per litter basis provides a challenge for using these data in regulatory decisions relating to risk characterization of TCE, TCA, and DCA. Also, the lack of clear dose-related effects (Dawson et al., 1993, and the present study) provide data of questionable utility for risk assessment applications."

Comments on Specific Types of Heart Defects Reported

While there were similar methods used for examining fetuses in the Dawson/Johnson laboratories involved and Dr. Johnson collaborated on the Fisher et al (2001) study, there were several differences between the 3 studies as noted in the EPA review (see table 1). In addition, preparation of the heart for dissection also differed. Dawson et al (1993) and Johnson et al (2003) both removed the heart first, then flushed with a fixative, while Fisher et al (2001) flushed the heart in situ via the left ventricle with a staining solution for better visualization (1:3 hematoxylin-saline solution), perhaps a more physiologically normal situation, then removed the heart and immersion fixed it in 10% buffered formalin.

Table 1. Comparison of Methods Used in the Dawson et al (1993), Johnson et al (2003), and Fisher et al (2001)

Study	Stock of animals	Source of animals	Route of exposure	Dose	Vehicle	Treatment days GD	Day of sperm GD	Day of sacrifice GD	Heart preparation
Dawson et al 1993	Sprague Dawley	Harlan, Indianapolis?	Drinking water	1.5 and 1100 ppm	Tap water	1-22	1?	22?	flushed with 2% glutaraldehyde after heart removal, fixed for 24 hrs in the same solution, transferred to 0.1 mol/L phosphate buffer

[1] Fisher et al. (2001) used soybean oil as a vehicle for TCE and retinoic acid (positive control) and treated the animals with a daily bolus gavage (GD 6-15). Johnson et al. (2003) used water as a vehicle for TCE, provided ad lib in the drinking water, which was changed daily with fresh TCE. The treatment period was over the entire 22-day pregnancy.

Johnson et al 2003	Sprague Dawley	Harlan?	Drinking water	2.5 & 250 ppb, 1.5 & 1100 ppm	Distilled water	1-22	1?	22?	flushed with 10% formalin, transferred to 10% formalin
Fisher et al 2001	Sprague Dawley	Charles River, Raleigh	Gavage	500 mg/kg	Soybean oil (TCE & RA); IERO* water (TCA, DCA)	6-15	0	21	flushed in situ via the left ventricle with staining solution for better visualization (1:3 hematoxylin-saline solution), then removed and immersion fixed in 10% buffered formalin

* IERO = ion exchange/reverse osmosis

The major difference in the data from the Dawson/Johnson laboratory vs. the Fisher laboratory appears to be the incidence of atrial septal defects (Table 2). The types of atrial septal defects are not detailed in any of the papers except for the statement that they are "secundum in type" (Dawson et al, 1993). Since the septum primum and septum secundum both grow rapidly around the time of birth to close the foramen ovale (Momma et al, 1992), this may represent a variation in development like other structures that are developing around the time of birth in the rat, e.g., skeletal ossification of sternebrae, vertebrae centra, etc., and the renal papillae. Whether the different methods of flushing the hearts may have disturbed the position of the septum which would not be closed on the day of sacrifice is unclear. Even more disturbing, however, is that neither Dawson et al (1993) nor Johnson et al (2003) provide maternal or fetal weight data, so it is impossible to know whether there were differences in fetal weight that would suggest a delay in development. Also, data on other aspects of fetal development (e.g., skeletal ossification) were not presented to give any clues about developmental stage. Fisher et al (2001) report no significant difference from water controls in maternal weight, uterine weight, number of implantations or fetal weight for TCE at 500 mg/kg. In that study, the percent of fetuses with atrial septal defects was approximately the same in the two groups. Thus, there are many unanswered questions about the incompleteness of the data presented in the Dawson et al. (1993) and Johnson et al. (2003) papers, in addition to the obvious design flaws and protracted length of time over which the studies were conducted. Without concurrent control data, it is very difficult to evaluate small changes in heart development that may or may not be related to TCE exposure.

Table 2. Comparison of Atrial Septal Defects in the Three Papers*

Study/Data	**Treatment Groups**						
Dawson et al 1993	**Control Tap water**	**TCE – Pre only 1.5 ppm**	**TCE – Pre only 1100 ppm**	**TCE – Preg only 1.5 ppm**	**TCE – Preg only 1100 ppm**	**TCE – Pre & Preg 1.5 ppm**	**TCE – Pre & Preg 1100 ppm**
No. of atrial septal defects/no hearts examined (%)	1/232 (0.4)	3/130 (2.3)	7/147 (4.8)	4/181 (2.2)	7/105 (6.7)	5/256 (2.0)	19/435 (4.4)

Johnson et al 2003	**Control Distilled water**	**TCE – 2.5 ppb**	**TCE – 250 ppb**	**TCE – 1.5 ppm**	**TCE – 1100 ppm**		
No. of atrial septal defects/no hearts examined (%)	7/606 (1.2)	0/144 (0)	1/110 (1.0)	4/181 (2.2)	7/105 (6.7)		
Fisher et al 2001	**Control IERO** Water**	**TCA 300 mg/kg in IERO water**	**DCA 300 mg/kg in IERO water**	**Control Soybean oil**	**TCE 500 mg/kg in soybean oil**	**Retinoic acid – 15 mg/kg in soybean oil**	
No. of atrial septal defects/no hearts examined (%)	2/273 (1.0)	2/269 (1.0)	3/298 (1.0)	6/367 (1.6)	4/290 (1.4)	3/155 (1.9)	

*Highlighted boxes are the same data reported in both papers
**IERO = ion exchange/reverse osmosis

Later, Robustly-designed Studies in Animals Fail to Confirm Earlier Findings of Malformations in Rats

A subsequent publication (Fisher et al., 2001) specifically investigated the cardiac teratogenic potential of TCE, TCA, and DCA in groups of 19 – 20 pregnant Sprague-Dawley rats. The rats received oral bolus doses of TCE (500 mg/kg/day, in soybean oil), TCA (300 mg/kg/day, in water) or DCA (300 mg/kg/day, in water) on gestational days 6 –15. On gestational day 21, fetuses were removed by laparohysterectomy and hearts were examined and microdissected under a stereomicroscope by an investigator experienced in the procedure (Dr. Paula Johnson, author of the earlier report that TCA caused cardiac effects at 291 mg/kg/day). The rates of cardiac malformations among treated animals did not differ from control rates.

Some early studies of TCA and DCA in pregnant Long-Evans rats (Smith et al., 1989, 1992) reported ocular malformations. In a study that reported findings after examination of the heads of the fetuses from the Fisher et al. 2001 study described above, Warren et al. (2006) reported that TCE, TCA, or DCA did not elicit gross ocular malformations. Morphometric analysis of the lens area, globe area and interocular distances revealed reductions of these parameters only in the TCA- and DCA-treated fetuses, but the overall smaller sizes of the fetuses in those groups were sufficient to explain the reductions.

An inhalation study of TCE in pregnant Charles River CD IGS rats (Carney et al., 2001; 2006) exposed groups of 27 animals to filtered air or to atmospheric concentrations of TCE up to and including the limit dose (600 ppm) for 6 hours/day on each of gestational days 6 – 20. Although maternal toxicity (decreased body weight gain) was elicited at the highest dose, TCE exposure caused no increase in gross, skeletal, or visceral (including heart and eye) malformations.

Assessment

Early findings of potential heart defects in rat pups associated with high doses of TCE metabolites during gestation prompted a series of investigations into the issue. The currently existing human data are deficient for risk assessment, but even so they do not support an association between TCE exposure and cardiac defects in babies. Data from GLP compliant animal studies that were carefully

designed to probe the existence of potential links between TCE or its metabolites and heart or eye defects have shown no associations at exposure levels that are several orders of magnitude higher than those that are environmentally or occupationally relevant.

The current EPA review of TCE toxicity focuses on several endpoints for establishing a reference concentration and a reference dose. These were considered the most sensitive effects in the current data base. Two of these are developmental endpoints: fetal heart malformations in rats and developmental immunotoxicity in mice. The current preliminary review focuses on the fetal heart malformations, since this appears to be an area with some controversy.

The EPA has developed an RfC of 0.001 ppm and an RfD of 0.0004 mg/kg/day. The fetal heart malformation data reported in Johnson et al. (2003) is used to support both of these values (US EPA, 2009; see Tables 5.1.23 and 5.1.24 and the associated text).

Studies from the Dawson/Johnson laboratory are clearly compromised by a number of design weaknesses which are stated in the EPA review, but the weight of evidence discussion in section 4.7.3.3.2.3 only considers those studies that reported cardiovascular defects and essentially ignores more carefully designed state-of-the art studies that do not report cardiovascular defects. This is not a "weight of evidence" evaluation but a "strength of evidence" evaluation. All the focus is on those studies that found an effect and none on the strengths and weaknesses of those that did not. There is nothing in the EPA weight of evidence about the studies that did not find cardiac defects but which used sound methodology, i.e., Fisher et al., 2001, and Carney et al., 2006. Weight of evidence clearly must consider all of the data, both positive and no effect data. When studies with clear flaws that use methods giving results not replicable in other laboratories constitute the majority of the positive data, it is difficult to see how the EPA can justify using these data as the basis for regulatory end-point(s).

Final Comments

The EPA Review Draft (pp 855-857) notes that potential limitations of the cardiac malformation data base have been raised. Nevertheless, EPA considers the animal data provide "strong, but not unequivocal, evidence" of TCE-induced cardiac malformations; and EPA's final evaluation is that there is sufficient concern regarding the potential for TCE to lead to cardiac defects (p 861).

EPA puts emphasis on the Johnson et al. (2003) and Dawson et al. (1993) studies and has noted that Johnson "has provided individual litter incidence data to the USEPA for independent statistical analysis (P. Johnson, personal communication, 2008) (see Section 6, dose-response)" (US EPA, 2009, p 857). It is unclear why EPA refers to "Section 6, dose-response" regarding this additional data. Nothing in this section described these data or how they were used. Hopefully, EPA has examined these data, although it is unclear if this has ever been done or how it has been incorporated into EPA's risk assessment.

Finally, there has been too much focus on one set of studies that show a putative positive response to low-exposure levels of TCE, without considering the overall data base and the limitations of the focus studies. The Johnson et al. (2003) and Dawson et al. (1993) studies have significant limitations regarding the reporting of standard maternal and fetal parameters. Without evaluating all of the maternal and fetal parameters, it is not possible to get a clear idea of how the animals are responding to treatment and whether the endpoint values are within historical ranges. Studies where major components of the results are not reported or the missing data has not been evaluated by the risk assessors may be useful in supporting other, more complete, data sets, but are of questionable value as a primary study in establishing an exposure standard.

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Supplement to Final Comments of Dr. Kathleen Gilbert, OPPT Draft Risk Assessment Peer Review Panel Member

September 5, 2013

1. Spotting Chemical Fact Sheet
2. DTSC Spotting Chemical for Web
3. Material Safety Data Sheet: Fast – PR
4. Material Safety Data Sheet: Picrin

DEPARTMENT OF TOXIC SUBSTANCES CONTROL

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Safer Spotting Chemicals

Best Practices for Textile Cleaning -- May 2007

Why and how are POG spotting chemicals used?

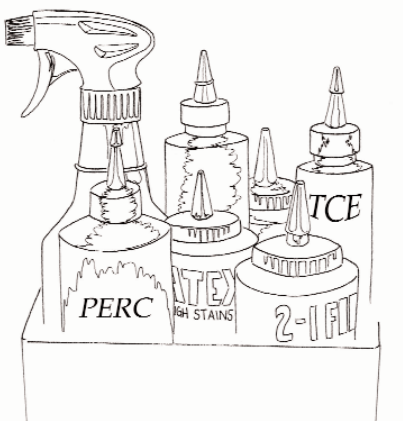
Paint, Oil and Grease (POG) spotting agents are used to remove spots from garments by professional textile cleaners. They are sprayed on spots before and after garments are processed through the garment cleaning machine.

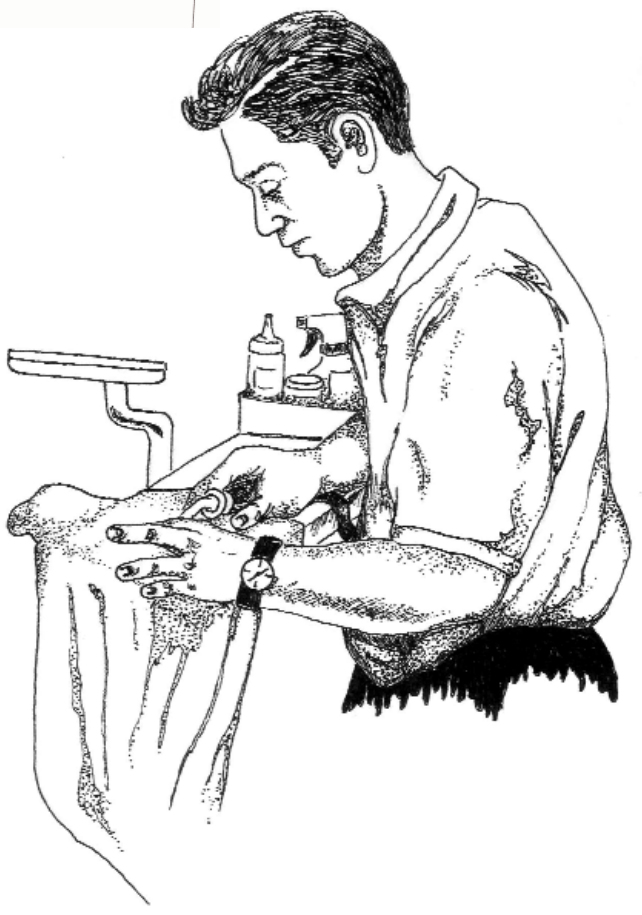
What are the commonly used POG spotting agents?

POG spotting agents containing trichloroethylene (TCE) and perchloroethylene (PERC) are used widely by the garment cleaning industry.

What are the toxicity problems with these spotting agents?

TCE and PERC are carcinogens and are heavily regulated in California. Spotters and other employees in garment cleaning plants are exposed to these dangerous chemicals.



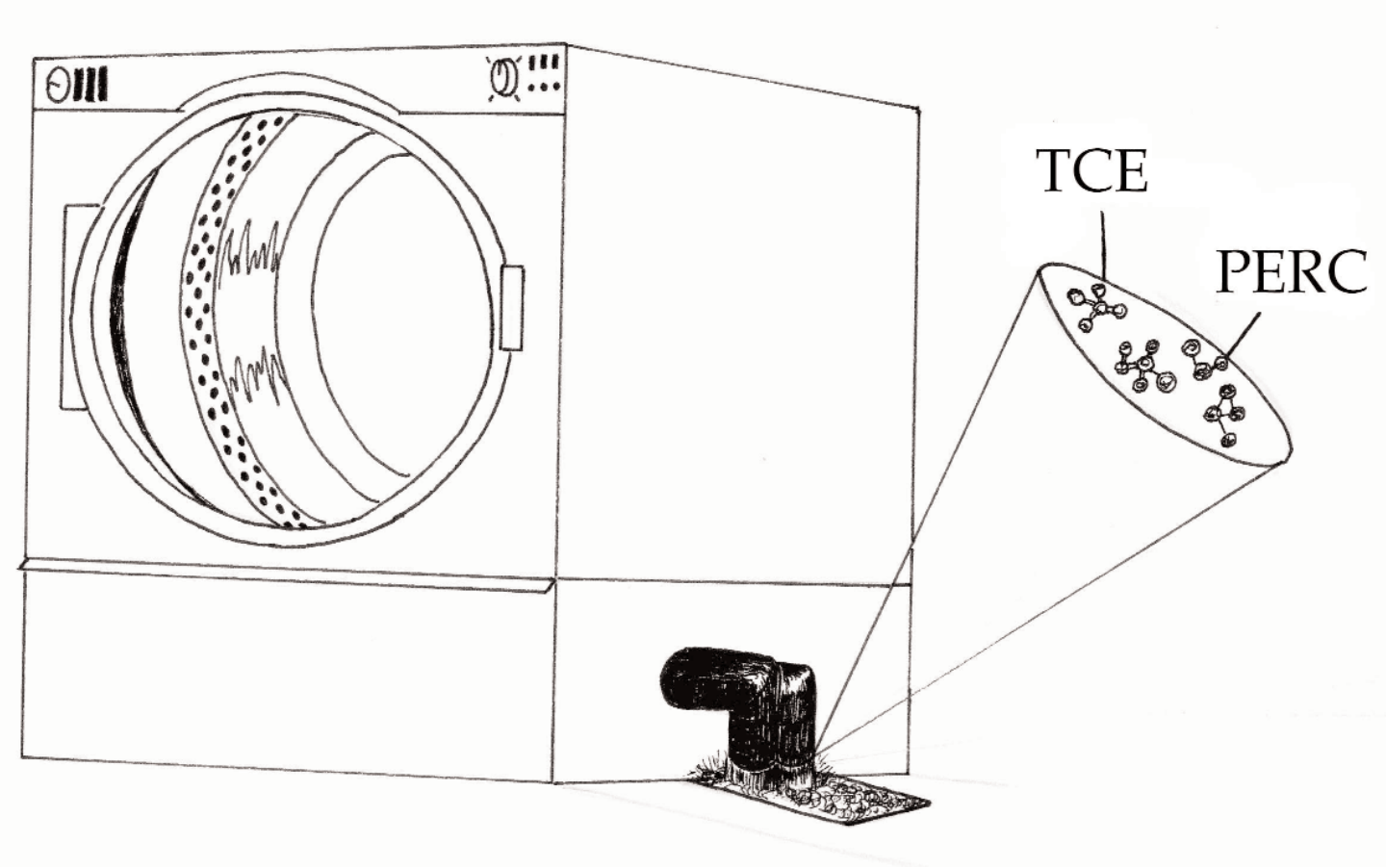


How do these spotting agents affect non-PERC garment cleaning processes?

Many cleaners have converted away from PERC dry cleaning to safer alternative processes. A number of them, however, continue to use TCE and PERC spotting agents. Use of these spotting agents will make the waste streams generated by the non-PERC garment cleaning processes hazardous.

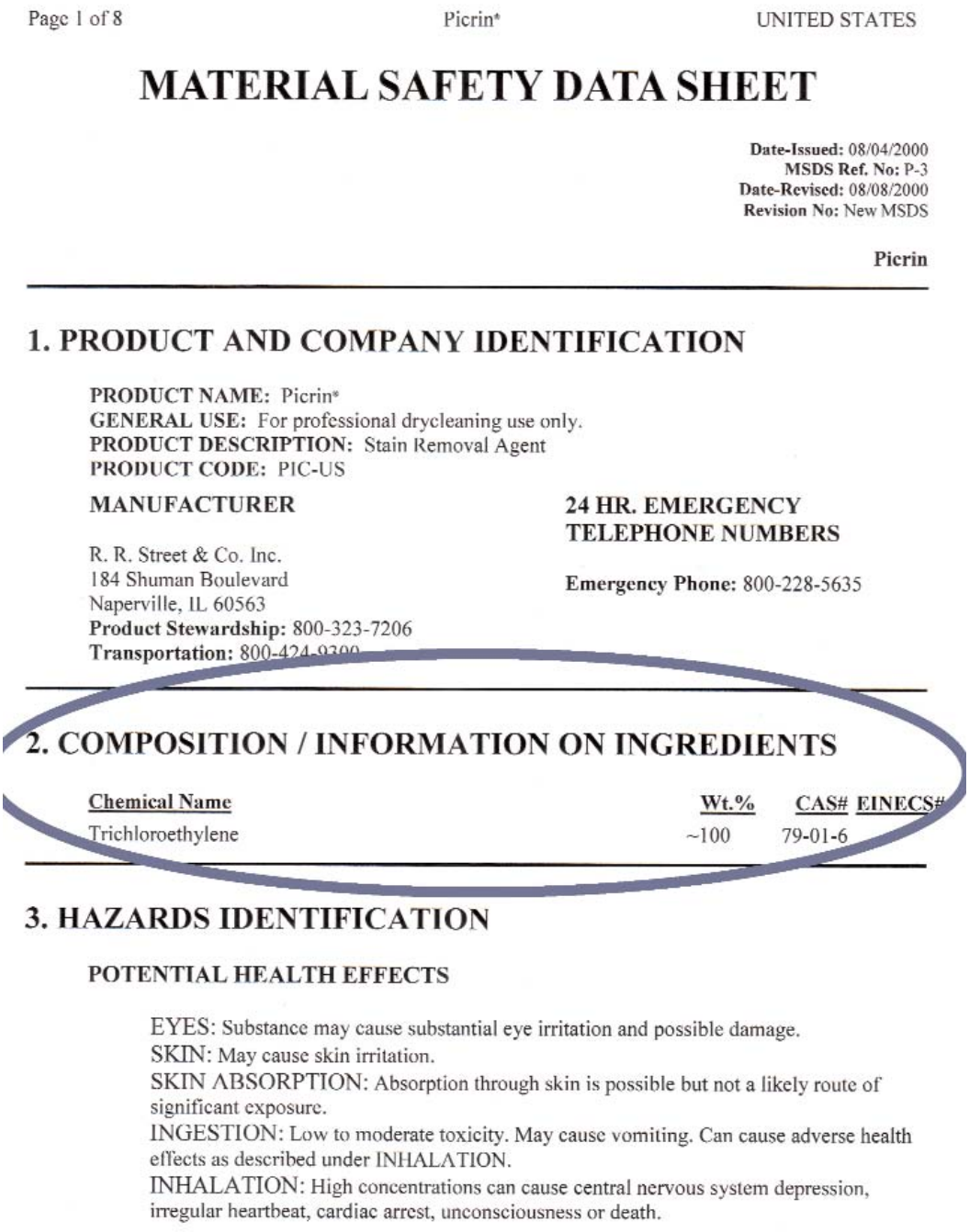
Is there a particular problem with these spotting agents for wet cleaning plants?

When cleaners pre-spot garments, the TCE and PERC residues are flushed into the sewer when the water from the cleaning process is discharged. It is illegal for cleaners to discharge hazardous waste to the sewer.



How do I know if my spotting agent contains TCE or PERC?

Ask your spotting chemical supplier for a Material Safety Data Sheet (MSDS) for the spotting agent. If the spotting agent contains TCE or PERC, it should list the chemical under the second section of the MSDS sometimes labeled "Composition / Information on Ingredients" or “Components.” The Chemical Abstract Service (CAS) number should also be listed. This is important because suppliers may call TCE and PERC by different names, but the CAS number stays the same. The CAS number for TCE is 79-01-6 and for PERC 127-18-4. The first page of an MSDS containing TCE is shown below. The “Composition / Information on Ingredients” section is circled in blue.



Page 1 of 8 Picrin® UNITED STATES

MATERIAL SAFETY DATA SHEET

Date-Issued: 08/04/2000
MSDS Ref. No: P-3
Date-Revised: 08/08/2000
Revision No: New MSDS

Picrin

1. PRODUCT AND COMPANY IDENTIFICATION

PRODUCT NAME: Picrin®
GENERAL USE: For professional drycleaning use only.
PRODUCT DESCRIPTION: Stain Removal Agent
PRODUCT CODE: PIC-US

MANUFACTURER

R. R. Street & Co. Inc.
184 Shuman Boulevard
Naperville, IL 60563
Product Stewardship: 800-323-7206
Transportation: 800-424-9300

24 HR. EMERGENCY TELEPHONE NUMBERS

Emergency Phone: 800-228-5635

2. COMPOSITION / INFORMATION ON INGREDIENTS

Chemical Name	Wt.%	CAS#	EINECS#
Trichloroethylene	~100	79-01-6	

3. HAZARDS IDENTIFICATION

POTENTIAL HEALTH EFFECTS

EYES: Substance may cause substantial eye irritation and possible damage.
SKIN: May cause skin irritation.
SKIN ABSORPTION: Absorption through skin is possible but not a likely route of significant exposure.
INGESTION: Low to moderate toxicity. May cause vomiting. Can cause adverse health effects as described under INHALATION.
INHALATION: High concentrations can cause central nervous system depression, irregular heartbeat, cardiac arrest, unconsciousness or death.

Have safer alternative spotting agents been tested?

The Institute for Research and Technical Assistance (IRTA) is a technical nonprofit organization. During a project sponsored by California Environmental Protection Agency's Department of Toxic Substances Control (DTSC) and U.S. EPA Region IX, IRTA tested low-VOC safer alternatives with a number of textile cleaning facilities using a range of different textile cleaning processes. IRTA and the test facilities found that the alternative POG spotting agents worked effectively.

Are the safer alternative POG spotting agents available?

There are some alternative spotting agents on the market. Many of these contain other ingredients that are toxic or are Volatile Organic Compounds (VOCs) that contribute to smog. The best alternatives from an overall health and environmental standpoint are water-based and soy based products.

Where can I get more information?

The IRTA report is on IRTA's website at www.irta.us, the DTSC's website at www.dtsc.ca.gov/PublicationsForms and the Western Regional Pollution Prevention Network website at www.wrppn.org.

You can contact IRTA at (818) 244-0300 with questions on spotting agent alternatives.

Some Products Containing TCE or PERC

Picrin® -- R.R. Street & Co. Inc.

2-1 Formula® -- R.R. Street & Co Inc.

Volatile Dry Spotter (V.D.S.) -- Laidlaw Corp.

Wetspo -- Laidlaw Corp.

Fast P.R.® -- Caled Chemical

PURO® -- Adco Inc.

P.O.G. -- Pariser Industries Inc.

TarGo® -- A.L. Wilson Chemical Co.

DEPARTMENT OF TOXIC SUBSTANCES CONTROL

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Spotting Chemicals: Alternatives to Perchloroethylene and Trichloroethylene in the Textile Cleaning Industry

Prepared by:
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Institute for Research and Technical Assistance

Prepared for:
Cal/EPA's Department of Toxic Substances Control and
U.S. Environmental Protection Agency Region IX

January 2007

DISCLAIMER

This report was prepared as a result of work sponsored and paid for by California Environmental Protection Agency's (Cal/EPA's) Department of Toxic Substances Control (DTSC) and the United States Environmental Protection Agency (U.S. EPA). The opinions, findings, conclusions and recommendations are those of the authors and do not necessarily represent the views of the sponsors. Mention of trade names, products or services does not convey and should not be interpreted as conveying Cal/EPA, DTSC or U.S. EPA approval, endorsement or recommendation. DTSC, U.S. EPA, their officers, employees, contractors and subcontractors make no warranty, expressed or implied, and assume no legal liability for the information in this report. The sponsors have not approved or disapproved this report nor have the sponsors passed upon the accuracy or adequacy of the information contained herein.

ACKNOWLEDGMENTS

The analysis in this report benefited considerably from the efforts of many persons within and outside the Institute for Research and Technical Assistance (IRTA). We would particularly like to acknowledge the valuable contributions made by Robert Ludwig from DTSC and John Katz from U.S. EPA. We are especially grateful to Dr. Julia Quint from the Department of Health Services Hazard Evaluation System & Information Service for her work in evaluating the toxicity of the materials. We would also like to give special thanks to certain suppliers who provided the materials for spotting agent alternatives. We are very thankful to the textile cleaning facilities who assisted us in testing the alternative spotting agents. Finally, we are indebted to Amy Blume of IRTA for her assistance in preparing the document.

EXECUTIVE SUMMARY

Perchloroethylene (PERC) and trichloroethylene (TCE) are used in the textile cleaning industry as Paint, Oil and Grease (POG) spotting agents. Spotting agents are used before or after cleaning in equipment to remove spots on garments. PERC and TCE are carcinogens. They are classified as Hazardous Air Pollutants by EPA and Toxic Air Contaminants by the California Air Resources Board. Both chemicals are listed on California's Proposition 65 and are listed hazardous wastes under the Resource Conservation and Recovery Act.

This project was sponsored by Cal/EPA's Department of Toxic Substances Control and the U.S. Environmental Protection Agency. It was conducted by the Institute for Research and Technical Assistance (IRTA), a nonprofit organization. The purpose of the project was to identify, test, develop and demonstrate low-VOC, low toxicity alternates to PERC and TCE POG spotting agents.

IRTA tested safer alternative spotting agents with seven textile cleaning facilities that have adopted alternatives to PERC dry cleaning. The alternative spotting agents were used in facilities that have hydrocarbon, Green Earth, carbon dioxide and water-based cleaning processes. The alternatives were used by each facility for one to five weeks on the facility garments.

The alternative spotting agents that proved to be effective are shown in Table E-1. One of the spotting agents, Cold Plus, is a commercial spotting product introduced to the market in the last year or so. The other spotting agents are cleaners that IRTA has tested successfully for other purposes.

Table E-1
Alternative Spotting Agents That Performed Effectively

Spotting Agent	Type of Material
Cold Plus	Water-Based Cleaner
Mirachem NP 2520	Water-Based Cleaner
Soy Gold 2500	Methyl Ester and Surfactants
DPM	Glycol Ether
90% Soy Gold 2500/10% Acetone	Blend
90% Soy Gold 2500/10% DPM	Blend
90% DPM/10% Acetone	Blend

IRTA conducted a cost analysis to compare the cost of using TCE spotting agents with the cost of using the alternatives. The results indicated that the cost of using the alternatives is lower than the cost of using TCE.

Waste streams from the textile cleaning process containing PERC or TCE are classified as hazardous waste. One of the advantages of using the alternative spotting agents is that

these waste streams may not be classified as hazardous waste. Another advantage is that workers and consumers would not be exposed to PERC or TCE during spotting of or in the wearing of the garments. The Department of Health Services Hazard Evaluation System & Information Service assisted IRTA in evaluating the toxicity of the alternative spotting agents based on their Material Safety Data Sheets. The findings indicate that the alternatives are lower in toxicity than PERC or TCE spotting chemicals.

This project demonstrates that there are a variety of effective cleaners that could be used as alternatives to PERC and TCE spotting agents in the textile cleaning industry. These include water-based cleaners, soy based cleaners, glycol ethers, acetone and blends of these cleaners.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

I. INTRODUCTION AND BACKGROUND

According to the California Air Resources Board (CARB), there are about 5,000 textile cleaning facilities in California. About two-thirds of these facilities use perchloroethylene (PERC) for dry cleaning garments. Approximately one-third of the cleaners in California have converted from PERC to various alternatives. The vast majority of the cleaners have adopted hydrocarbon. However, other technologies, including Green Earth which is a silicone based solvent, Rynex which is a glycol ether, carbon dioxide and water-based technologies that rely on water and detergent are also being adopted for textile cleaning.

Regardless of the technology that cleaners employ, they all perform spotting as part of the garment cleaning process. Cleaners use spotting agents to remove spots prior to cleaning the garments in the machine or after the garments have been cleaned in the machine. Many of the spotting agents historically contained PERC and now contain trichloroethylene (TCE). Both PERC and TCE are carcinogens, they are classified as Hazardous Air Pollutants (HAPs) by EPA, they are classified as Toxic Air Contaminants (TACs) in California, they are listed on Proposition 65 as substances known to cause cancer to the state of California and they are listed hazardous wastes under the Resource Conservation and Recovery Act (RCRA).

The Institute for Research and Technical Assistance (IRTA) is a nonprofit organization established in 1989. IRTA works with companies and whole industries to identify, test, develop and demonstrate low-VOC, low toxicity solvent alternatives. Under U.S. EPA's Pollution Prevention Grants program, Cal/EPA's Department of Toxic Substances Control contracted with IRTA to identify, develop, test and demonstrate safer spotting agents for textile cleaning.

PREVIOUS RELATED WORK

Over the last three years, IRTA completed two projects related to the current spotting chemical investigation. The first project, sponsored by CARB and U.S. EPA, was a technology assessment of alternatives to PERC dry cleaning. Part of this project involved sampling certain of the waste and effluent streams for some of the alternative cleaning methods. In some of the streams, IRTA identified TCE and PERC. CARB is currently proposing a phaseout of PERC dry cleaning in 2023 so cleaners in the state will be converting to alternative technologies increasingly over the next 15 years.

The second project, sponsored by DTSC, involved examining the characteristics of the hydrocarbon technology, the most widely used PERC alternative, in more detail. IRTA sampled waste streams from the hydrocarbon process and, again, found PERC and TCE. Although the PERC may have entered the waste streams from various sources, the obvious source of the TCE was spotting chemicals.

Since PERC and TCE are listed hazardous wastes, if they are present in a waste stream, the stream is classified as hazardous waste. Some waste and effluent streams generated from the PERC cleaning alternatives would not be classified as hazardous waste if they did not contain these substances. In addition, it could be less costly to dispose of these wastes if they did not contain PERC or TCE. As cleaners convert away from PERC dry cleaning over the next several years, it is important to eliminate PERC and TCE in spotting chemicals as well.

PROJECT APPROACH

Virtually all cleaning facilities, regardless of the cleaning technology they have, use so-called Paint, Oil and Grease or POG spotting agents for spotting garments. These spotting agents contain various solvents but the most widely used POGs contain TCE and there are others that contain PERC.

The motivation for this project was to find effective alternative POG spotting agents that do not contain PERC or TCE. One of the aims of the project was to find alternatives that are low in VOC content and have low toxicity. There are alternative POG spotting agents that do not contain PERC but cleaners do not believe they work effectively. IRTA identified several existing POG spotting agents that do not contain PERC or TCE but, in many cases, it is not clear what chemicals they do contain. Many of the suppliers claim trade secrets on the Material Safety Data Sheets (MSDSs) and IRTA did not want to test spotting agents that have unidentified components.

Because cleaners do not accept existing products and because it is not clear what materials are in existing products, IRTA tested only one existing product, a water-based cleaner. IRTA tested several other products and developed blends of other products used in different industries for cleaning. IRTA tested these alternatives in screening tests and selected the best seven cleaners for more extensive testing in cleaning facilities. IRTA worked with seven cleaners to test the alternatives and the cleaners used a variety of PERC dry cleaning alternative processes. IRTA wanted to make sure the alternative spotting agents would be effective for all of the alternative technologies that cleaners will adopt over the next several years.

STRUCTURE OF DOCUMENT

Section II of the document presents information on the waste stream analysis conducted in the earlier two projects. It describes the spotting procedure in more detail and identifies the POG spotting agents used today. Section III summarizes the alternatives that were tested and the tests that were conducted. The health and environmental characteristics of the current spotting agents and the alternatives are described in Section IV of the document. The section presents information on the regulations, the VOC content and the toxicity of the spotting agents used today and the alternatives. Finally, Section V summarizes the results and conclusions of the analysis.

II. SPOTTING AGENT CHARACTERISTICS

This section presents information on the spotting agents found in the waste and effluent streams in the textile cleaning industry. It focuses on relevant aspects of the analysis of the waste and effluent streams from IRTA's earlier CARB/U.S. EPA and DTSC projects. It then discusses the procedures used in spotting. Finally, it presents information on some of the current POG spotting agents used by cleaners throughout the industry.

WASTE AND EFFLUENT GENERATION AND RESULTS

The major alternatives to PERC dry cleaning are:

- Hydrocarbon dry cleaning;
- Green Earth, a silicone based dry cleaning process;
- Rynex, a glycol ether based dry cleaning process;
- Carbon dioxide cleaning; and
- Various water-based cleaning methods include traditional wet cleaning which involves immersing garments in water and detergent, icy water cleaning which is conducted with low temperature water and detergent and Green Jet which involves spraying garments with a water mist and detergent.

The hydrocarbon, Green Earth and Rynex processes use filters to remove particulate contaminants in the dry cleaning process. The filters or filter residue is disposed of as waste. These processes also often use distillation to separate the oily contaminants from the solvent; this results in a still bottom that is disposed of as waste. Finally, there is water present in the systems from a variety of sources. The water and solvent are physically separated and the solvent is reused in the process. The water, which still contains some solvent, is a waste stream. Most cleaners use evaporation to dispose of this separator water.

In the carbon dioxide process, there is no separator water but a still bottom containing a high concentration of detergent is generated. In the water-based cleaning processes, the wash and rinse effluents are discharged to the sewer.

Waste and Effluent Analysis From CARB/U.S. EPA Project

In the earlier project, IRTA worked with the Los Angeles County Sanitation Districts (LACSD) to analyze the waste and effluent streams. IRTA collected samples from facilities using alternative technologies and LACSD analyzed the samples in their lab.

IRTA and LACSD analyzed the samples for various components including toxic volatile and semi-volatile organics. LACSD used EPA Test Methods 601/602 or 624 for the volatile organics and EPA Test Method 625 for semi-volatile organics. PERC and TCE are toxic volatile organics.

The analysis results for the still bottoms and separator water for the Green Earth, hydrocarbon and Rynex processes and for the still bottoms for the carbon dioxide process indicated that there were no toxic volatile and semi-volatile components found above detection levels. This does not mean PERC and TCE were not present, however, because the samples were very dirty. As a result, LACSD had to dilute them substantially to analyze them and this may have reduced the concentration of volatiles to below detection levels.

IRTA also sampled the wash and rinse effluents from four facilities using water-based cleaning technologies in two rounds of sampling. In the first round of sampling, the results indicated that PERC or TCE were found in the effluent at three of the facilities. The results are shown in Table 2-1.

Table 2-1
Water-Based Cleaning Effluent Results--First Round Sampling

Facility	Toxic Organics (micrograms per liter)			
	PERC		TCE	
	Wash	Rinse	Wash	Rinse
Wet Cleaner #1	5,300	1,100	<200	<40
Wet Cleaner #2	<40	<40	5,100	3,200
Wet Cleaner #3	<200	<40	<200	<40
Wet Cleaner #4	<1,000	140	<1,000	<40

Note: Different dilutions were required for each facility so detection limits were also different.

The values in Table 2-1 that have the "less than" (<) sign in front of them are below the detection level. The values are different for different cleaners because different dilution levels were required. Taking this into account, three of the wet cleaners had PERC or TCE in the effluent streams that were above detection levels. Wet Cleaner #1 had high concentrations of PERC in both the wash and rinse effluent. Wet Cleaner #2 had high concentrations of TCE in both the wash and rinse effluent. Wet Cleaner #4 had PERC in the rinse effluent.

IRTA investigated further to determine the origin of the PERC and TCE in the effluent streams. Wet Cleaner #1 and Wet Cleaner #4 both had a wet cleaning machine and a PERC dry cleaning machine. Wet Cleaner #2 and Wet Cleaner #3 had only wet cleaning machines. Wet Cleaner #4 was using spotting chemicals containing PERC and Wet Cleaner #2 was using spotting chemicals containing TCE.

Table 2-2 presents the results of the second round of sampling. Before the second round of sampling, Wet Cleaner #1 removed the PERC machine and the spotting and finishing supervisor was replaced. PERC and TCE were found in the wash effluent. The new spotter may have begun using a TCE based spotting chemical. Wet Cleaner #2 stopped using the TCE based spotting agent when IRTA reported the results. No TCE was found in the second round of sampling at this facility. Wet Cleaner #4 removed the PERC

machine before the second round of sampling. Even so, PERC was still found in the wash and rinse effluents and might be present in the spotting chemicals.

Table 2-2
Water-Based Cleaning Effluent Results--Second Round Sampling

Facility	Toxic Organics (micrograms per liter)			
	PERC		TCE	
	Wash	Rinse	Wash	Rinse
Wet Cleaner #1	480	<100	510	<100
Wet Cleaner #2	<20	<20	<20	<20
Wet Cleaner #3	<200	<200	<100	<100
Wet Cleaner #4	83	82	<20	<20

Note: Different dilutions were required for each facility so detection limits were also different

Waste Analysis for DTSC Project

This project focused in more detail on the hydrocarbon alternative process which is being adopted widely by cleaners. IRTA sampled the sludge/still bottom and the separator water at eight hydrocarbon facilities. The DTSC Hazardous Materials Laboratory (HML) analyzed the samples for the presence of VOCs. The method used by HML was EPA Method 8260B "volatile organic compounds by GC/MS."

A number of VOCs were present in the waste streams. Table 2-3 presents the results of the analysis for PERC and TCE. The figures show that PERC and/or TCE were present in at least one waste stream analyzed at each facility. In some cases, the concentrations were very high.

Table 2-3
PERC and TCE Found in Waste Stream Analysis at Hydrocarbon Cleaners

Facility	Separator Water Concentration (micrograms per liter)		Sludge Concentration (milligrams per kilogram)	
	PERC	TCE	PERC	TCE
#1	30,000	9,000	19	6
#2	230	2,400	1,900	400
#3	ND	ND	3	ND
#4	6	ND	30	ND
#5	71	ND	ND	ND
#6	ND	ND	130	ND
#7	17	2	2	ND
#8	16,000	ND	12	ND

Note: ND is non-detectable.

Summary of Analysis Results

The analysis results indicate that PERC and/or TCE are present in most waste and effluent streams in the textile cleaning industry. The PERC may come from a variety of sources. First, it can come in as a residue on garments that were previously dry cleaned using PERC. Second, cross contamination might occur in facilities with a PERC dry cleaning machine and another technology. Third, the PERC may be present in the spotting chemicals. The TCE comes from only one source, spotting chemicals. As discussed below, many POG spotting agents contain TCE and they are widely used.

SPOTTING PROCEDURES AND SPOTTING CHEMICALS

Cleaners use POG spotting agents to remove several types of contaminants before and sometimes after the garments have been cleaned in the machine. These spotting agents are suitable for removing:

- tar;
- ink;
- shoe polish;
- mascara;
- lipstick;
- oil-based paints;
- nail polish; and
- crayon.

A number of different solvents are used in POG spotting agents. These include glycol ethers, mineral spirits, methyl ethyl ketone, acetates and various alcohols. Cleaners often find these solvents to be ineffective and many spotters prefer spotting agents that contain PERC and/or TCE. As mentioned earlier, PERC was extensively used in spotting agents in the past. Because cleaners were aware that PERC was under increasing scrutiny in the dry cleaning industry, the spotting chemicals were reformulated with TCE. Although TCE is also toxic, the industry perceived it as being less toxic than PERC.

There are a handful of suppliers that provide POG spotting agents to the industry. These include R.R Street & Company, Laidlaw, Adco and Caled. These suppliers package the POG spotting agents in quantities ranging from one gallon containers to 55-gallon drums. Distributors purchase the spotting agents from the suppliers and sell them to cleaners. Distributors in California include United Fabricare, HNS, McGregor and MDL.

IRTA worked with cleaners and suppliers to estimate the amount of TCE and PERC containing spotting agents that are sold in California. About 42,000 gallons of the TCE based spotting agents are sold in California annually. The concentration of TCE in the spotting agents ranges from 10 percent to 100 percent. One of the most widely used spotting agents containing TCE is called Picrin (see below); it contains 100 percent TCE. Assuming that all of the spotting agents are TCE and not PERC, and assuming an average concentration of TCE of 95 percent for all products, about 40,000 gallons of TCE are used annually in spotting. The density of TCE is 12.11 pounds per gallon so this amounts to 242 tons of TCE per year. A much smaller amount of PERC based spotting agents are

used annually, according to the suppliers. IRTA estimates the amount of PERC spotting agents used annually in California at 150 gallons or about one ton per year.

Cleaners IRTA worked with to test the alternatives during this project described and illustrated the proper process for spotting with POG agents. The garment is put on the spotting board which is similar to an ironing board. The spotting agent is applied to the spot on the garment using a squeeze bottle. It is rubbed in with a brush or bone used for that purpose. The spot is flushed with water from the steam supply. It is then dried with compressed air. The garment is placed aside for the next load in the machine. In some cases, spotting is performed after the garments go through the machine when the cleaning process does not successfully remove the spot. The procedure is the same as that described above.

Specific TCE and PERC Spotting Agents

MSDSs for several spotting agents containing TCE and a few containing PERC are shown in Appendix A. The most widely used POG spotting agent is Picrin which is offered by R.R. Street & Company. A product sheet describing its use and an MSDS are shown in appendix A. The MSDS indicates that Picrin contains about 100 percent TCE.

An MSDS for a product called Volatile Dry Spotter (V.D.S.) offered by Laidlaw is shown in Appendix A. The MSDS indicates that the product contains approximately 98 percent TCE.

Another product, called Fast P-R, is offered by Caled. A product sheet and an MSDS for this product are shown in Appendix A. The MSDS indicates that the concentration of TCE in the product is approximately 95 percent.

Adco offers a product called PURO which apparently contains TCE. A product sheet and a description of the contents of the product from the State Coalition for Remediation of Drycleaners are shown in Appendix A. The contents sheet indicates that the concentration of TCE is less than 100 percent. Another product offered by Adco called Semi-Wet apparently contains 50 percent TCE. A product sheet and a content sheet description are shown in Appendix A.

A contents sheet from the State Coalition for Remediation of Drycleaners for an R.R. Street product called 2-1 Formula is shown in Appendix A. The contents sheet indicates that the product contains less than 50 percent TCE.

A contents sheet from the State Coalition for Remediation of Drycleaners for a product offered by Pariser Industries, Inc., is shown in Appendix A. According to the contents sheet, the product, called P.O.G., contains 21.8 percent PERC.

An MSDS for a product offered by Fabritec International, called 6748 VOL Volatile Spotter, is shown in Appendix A. According to the MSDS, the product contains between

30 and 60 percent of an unidentified halogenated hydrocarbon which is likely to be TCE or PERC.

A contents sheet from the State Coalition for Remediation of Drycleaners for a product offered by A.L. Wilson Chemical Co. called TarGo is shown in Appendix A. The product contains 10 percent TCE.

III. ALTERNATIVES TESTING

During this project, IRTA tested one alternative spotting agent that is used as a spotting agent commercially, some other cleaning agents used for cleaning in other industries and blends of the other cleaning agents developed by IRTA specifically for the testing. IRTA screen tested the alternative cleaners and then took them to cleaning facilities so they could be tested by spotters. This section describes the tests of the alternative cleaning agents in detail. It also presents a cost analysis and comparison of the current and alternative spotting agents.

SCREENING TESTS OF ALTERNATIVE SPOTTING AGENTS

The screening tests were conducted to determine what types of cleaning agents used in other industries might be suitable as alternatives to PERC and TCE based POG spotting chemicals. The approach that was used was to obtain garments from Goodwill and select garments for the screening tests that were made of a variety of different fabrics. Stains of the type that are removed during spotting with POG spotting agents were put on the garments. Baseline cleaners and a range of different cleaning agents were then tested to see if they could effectively remove the spots. IRTA relied on two experienced textile cleaners to conduct the spotting and to judge the comparative cleaning ability of the cleaners.

Garments and Contaminants Used in Screening Tests

Some of the garments used in the screening tests and the contaminants that were put on them were:

- white shirt that appears to be made of polyester with an Elite Security decal contaminated with blue screen printing ink;
- yellow men's pants made of nylon and polyester contaminated with motor oil;
- blue men's shirt made of 100 percent cotton contaminated with black latex paint;
- tan men's dockers made of 100 percent cotton contaminated with red nail polish;
- beige women's pants made of cotton and spandex contaminated with mascara;
- gold men's jacket made of acetate contaminated with a black Sharpie marker;
- beige men's shirt made of raw silk contaminated with lipstick;
- beige men's pajama pants made of acetate and rayon contaminated with rubber cement; and
- beige men's cargo pants made of 100 percent cotton contaminated with blue ballpoint pen ink.

Pictures of some of these garments with the stains from the contaminants are shown in Figures 3-1 through 3-7.

Figure 3-1. White Shirt with Blue Screen Printing Ink.

Figure 3-2. Yellow Pants with Motor Oil.

Figure 3-3. Blue Shirt with Black Latex Paint.

Figure 3-4. Tan Dockers with Red Nail Polish.

Figure 3-5. Beige Pants with Mascara.

Figure 3-6. Gold Jacket with Black Sharpie Marker.


Figure 3-7. Beige Shirt with Lipstick.

Two owners of cleaning facilities who are experienced spotters tested the alternative spotting agents on the Goodwill garments and on some of the garments in their cleaning facilities. One spotter at one of these facilities also assisted in the screening tests. The procedure that was used was to test the alternative cleaners on the spots and to use the proper spotting techniques (rinse with steam and blow out with air) described earlier. The baseline spotting agents were Picrin and Pyratex, two POG spotting agents commonly used today.

Cleaners Used in Screening Tests

IRTA selected several different cleaning agents for the screening tests. IRTA wanted to find alternative POG spotting agents that were low in VOC content and low in toxicity. IRTA also wanted to select cleaning materials that would not lead to the classification of the waste and effluent streams in textile cleaning as hazardous waste. Some of the cleaning agents tested during screening did not meet these requirements but IRTA tested them to see if they were effective enough cleaners to be used in smaller concentrations with other cleaners. The cleaning agents selected for screening tests were:

- Cold Plus;
- Mirachem NP 2520;
- PWF-10;
- Soy Gold 1000;
- Soy Gold 2500;
- C-29;
- Acetone;
- 90 percent Soy Gold 2500/10 percent acetone;
- 90 percent C-29/10 percent acetone;
- VM&P;
- DB; and
- 90 percent DB/10 percent acetone.

Cold Plus is the only commercial spotting agent that was tested; it is a water-based cleaner. Mirachem NP 2520 is a water-based cleaner developed for cleaning in the screen printing industry. PWF-10 is a water-based cleaner used to clean oil and grease in the auto repair industry. IRTA has tested Soy Gold 1000 and Soy Gold 2500 for cleaning ink in the screen and lithographic printing industries and they are used in other cleaning applications; they are based on methyl esters and they have low VOC content. C-29 is a mineral spirit based cleaner used for cleaning ink in the lithographic printing industry; like soy, it is low in VOC content. Acetone is used for cleaning in many applications and it is not classified as a VOC. If it is present in a cleaning agent at or above 10 percent, the spent cleaner would be classified as hazardous waste (see discussion in the next section). IRTA tested it to see if it cleaned effectively and could be used as an ingredient at 10 percent or less concentration in a spotting chemical. VM&P is a mineral spirits based cleaner that is classified as a VOC. Again, it was investigated as a possible ingredient in a spotting chemical. DB is a glycol ether that is considered to be a non-VOC in CARB's consumer product regulations (see discussion of regulations in next section).

Results of Screening Tests

The results of the screening tests showed that two of the three water-based cleaners performed relatively well in the screening tests and one did not. The Soy Gold 1000 is not water rinseable and it could not be rinsed with the steam; because it could leave a ring, IRTA did not test the chemical further. The C-29 and VM&P mineral spirits based cleaners did not perform well and IRTA did not use them further. Acetone at 100 percent was a reasonably effective cleaner but dissolved part of an acetate garment; it did not have a negative effect at 10 percent concentration. IRTA decided to test acetone, which is a good cleaner, at only a 10 percent concentration in the alternative spotting agents.

Based on these conclusions, the cleaning agents that were selected for further testing as a result of the screening tests are:

- Cold Plus;
- Mirachem NP 2520;
- Soy Gold 2500;

- DB;
- 90 percent Soy Gold 2500/10 percent DB;
- 90 percent Soy Gold 2500/10 percent acetone; and
- 90 percent DB/10 percent acetone.

MSDSs for these cleaners and the components of the cleaners are shown in Appendix B. Part way through the project, IRTA became aware that DB which is called diethylene glycol monobutyl ether, an ethylene glycol ether, has higher toxicity than the propylene glycol ethers. IRTA decided to substitute DPM, a propylene glycol ether called dipropylene glycol monomethyl ether, for DB. An MSDS for DPM is also shown in Appendix B.

FIELD TESTS OF ALTERNATIVE SPOTTING AGENTS

The field testing of the alternative spotting agents was conducted at seven facilities that have a total of nine cleaning machines. The facilities and the cleaning technologies for which the alternative spotting agents were tested are:

- Crown Cleaners--hydrocarbon machine;
- Porter Ranch Cleaners--hydrocarbon machine and wet cleaning machine;
- Flair Cleaners--hydrocarbon machine and wet cleaning machine;
- Larsen's Cleaners--Green Earth machine;
- Village Cleaners--Green Jet machine;
- Royal Cleaners--carbon dioxide machine; and
- Imperial Cleaners--icy water machine.

As discussed earlier, most cleaners that are converting away from PERC are adopting hydrocarbon so IRTA tested the alternative spotting agents at three facilities where hydrocarbon is being used. IRTA also tested the spotting agents at one facility using Green Earth and one facility using carbon dioxide. IRTA tested the alternative spotting agents at four facilities that have water-based cleaning technologies. These included two cleaners using the traditional wet cleaning technology, one cleaner that uses the Green Jet technology and one cleaner that uses the icy water technology.

Approach to Field Testing

At each of the facilities, IRTA first tested the alternative spotting agents on Goodwill garments and ran them through the machine. This was necessary to ensure that none of the alternative spotting agents would leave a ring after they were cleaned with each of the different technologies. IRTA selected alternative spotting agents originally with this in mind. All of the alternatives that were selected as a result of the screening tests were either water soluble or water rinseable. As discussed in Section II, if spotters use proper procedures, they will flush the spot with steam (water) after the spotting agent is applied and then dry it before cleaning it in the machine. Since all of the alternatives are water soluble or rinseable, IRTA expected they would not leave a ring if the spotting were performed properly. In all cases, with every technology, none of the alternative spotting

agents left a ring when spotting was performed properly. In some cases, when spotting was not performed properly, the spotting agents did leave a ring.

After IRTA tested the selected alternatives initially on the Goodwill garments at some of the facilities to ensure they would not leave spots, IRTA and the spotters tested them on the cleaner's garments. Generally one or more of the spotting agents performed better than others. IRTA observed that there were strong personal preferences and the preferred alternatives varied widely from facility to facility. IRTA provided larger quantities of the alternatives the spotters preferred and the spotters tested them routinely in scaled-up testing for one to five weeks on their garments in place of the POG spotting agent that are currently used. IRTA staff visited the facilities at least once a week during the testing to get feedback on the performance of the alternative spotting agents.

Results of Field Testing

Most of the owners or spotters who tested the alternatives thought that at least one of them was as good as the current POG spotting agent. All of the alternatives had some limitations but most owners and spotters indicated that even the POG spotting agents they use currently have limitations. This is why cleaners often use more than one POG spotting agent.

Table 3-1 shows the preferred spotting agents for the different facilities. One of the facilities, Larsen's, tested only one alternative in the scaled-up testing. Several of the facilities tested most of the alternatives for at least a week. The facilities that tested DB and DPM and blends containing the two chemicals generally thought DPM performed better than DB.

Table 3-1
Spotting Agents That Were Used and Performed Well in Scaled-Up Testing

Facility	Acceptable Alternative POG Spotting Agents
Crown	DB/acetone, soy/DB, Mirachem NP 2520
Porter Ranch	DB/acetone, soy/DB, soy/acetone, DB
Flair	DB/acetone, soy/DB, soy/acetone, DB, Mirachem NP 2520, soy/DPM
Larsen's	Soy
Village	Cold Plus, soy
Royal	DPM, Cold Plus, soy
Imperial	Cold Plus, soy/acetone, DPM

COST OF CURRENT AND ALTERNATIVE SPOTTING AGENTS

IRTA performed a limited cost analysis of the current spotting agents and the alternative spotting agents that were tested during this project. The baseline POG spotting agent used for the analysis was TCE. IRTA collected price information from suppliers for the price paid by cleaners for the spotting agent. The price ranged from about $42 to $50 per

gallon if the cleaner purchased the product in gallon quantities. The price of the alternative spotting agents was compared with TCE at a mid range price of $46 per gallon.

Cold Plus is the only alternative that was tested that is currently a commercial product sold to the textile cleaning industry as a spotting agent. One local distributor indicates that the price of the spotting agent purchased in one gallon quantities is $36 per gallon.

Three of the other alternative spotting agents, Soy Gold 2500, Mirachem NP 2520 and DPM, are commercial products sold for other applications but not currently sold as spotting agents to the textile cleaning industry. IRTA estimated the prices of these materials if purchased in one gallon quantities as spotting agents based on discussions with the suppliers of these chemicals and a company that would like to distribute them.

The Soy Gold 2500 can be purchased from the supplier at a price of $12.50 per gallon for drum quantities. Assuming the markup by the distributor would double the price charged to dry cleaners, the price of the Soy Gold 2500 for this industry would be $25 per gallon The Mirachem NP 2520 supplier price is $10 per gallon for drum quantities. Again, assuming the price would double from a distributor markup, the price of the Mirachem NP 2520 to dry cleaners would be $20 per gallon. IRTA did not further evaluate DB as an alternative spotting agent because it is more toxic than DPM. A supplier indicates that the price of DPM is $12.56 per gallon if purchased in drum quantities. Again assuming the distributor markeup would double the price, the price of DPM to the dry cleaner would be $25 per gallon.

For the other blends containing Soy Gold 2500, acetone and DPM, IRTA assumed the supplier would have to blend the chemicals before selling them in drum quantities to the distributor. IRTA obtained prices for the blended materials from a supplier. The blend of 90 percent Soy Gold 2500/10 percent acetone is priced at $12.57 per gallon based on purchases of drum quantities. Assuming the distributor markup would double the price, the cleaner would pay about $25 per gallon for the blend. For the blend of 90 percent Soy Gold 2500/10 percent DPM, the supplier estimated a price of $12.91 per gallon based on drum purchases. Again, assuming the distributor markup would double the price, a cleaner would pay $26 per gallon. For the blend of 90 percent DPM/10 percent acetone, the supplier would charge $11.76 per gallon based on drum purchases. The distributor markup would double the price to $24 per gallon.

Table 3-2 shows the cost comparison for the TCE based spotting chemicals and the alternatives tested in this project. Note that the analysis includes DPM rather than DB because DPM is lower in toxicity.

Table 3-2
Price Estimates of Current and Alternative Spotting Agents
Based on One Gallon Quantities

Spotting Agent	Price Per Gallon
TCE	$46
Cold Plus	$36
Soy Gold 2500	$25
Mirachem NP 2520	$20
DPM	$25
90% Soy Gold 2500/10% Acetone	$25
90% Soy Gold 2500/10% DPM	$26
90% DPM/10% Acetone	$24

The values of Table 3-2 show that the cost of the TCE based spotting chemicals is higher than the cost of all of the alternative spotting chemicals. Even if the distributor markup was substantially higher for the alternatives, they would still be less costly than TCE.

IV. HEALTH AND ENVIRONMENTAL CHARACTERISTICS OF ALTERNATIVES

This section describes the regulations that affect the alternatives and the toxicity of the alternatives. The DHS HESIS assisted IRTA in evaluating the toxicity of the alternatives based on the information on the MSDSs.

AIR REGULATIONS THAT APPLY TO SPOTTING CHEMICALS

In California, four or five suppliers sell spotting agents in large quantities to distributors. The distributors, in some cases, repackage the spotting agents in smaller quantities and sell them to cleaners along with other supplies like filters, hangers and dry cleaning agents. The local air districts have regulatory authority over spotting chemicals since they regulate VOCs and toxic materials used in industrial facilities. Textile cleaning operations are considered industrial facilities. CARB may also have regulatory authority over spotting chemicals. CARB and local air districts do not currently have regulations that affect spotting chemicals.

CARB and local air districts could regulate the VOC content of spotting chemicals. TCE is classified as a VOC but PERC is not classified as a VOC. Other components of the formulations containing TCE and PERC are classified as VOCs. These agencies could also regulate the use of spotting agents containing TACs. Both TCE and PERC are listed TACs; a few of the other components in some of the formulations are also classified as TACs. The regulatory agencies might forbid the use of spotting agents that contain chlorinated solvents like TCE or PERC, for example.

The alternatives that were tested during this project were selected to have low toxicity and low VOC content. Cold Plus and Mirachem NP 2520 are water-based cleaners that likely have low VOC content. Soy Gold 2500 alone and combined with glycol ethers and acetone, also has low VOC content, at less than 25 grams per liter. Acetone, an ingredient of the soy/acetone and DPM/acetone formulation, has a VOC content of zero since it is exempt from VOC regulations. The glycol ethers, DB and DPM, have high VOC content. In CARB's consumer product regulations, however, both glycol ethers would be classified as Low Vapor Pressure (LVP) materials. For purposes of the consumer product regulation, LVPs are considered to be non-VOCs. Local air districts, however, would regulate the glycol ethers as having very high VOC content.

WASTE REGULATIONS THAT APPLY TO SPOTTING CHEMICALS

TCE and PERC are listed hazardous wastes under RCRA. Both chemicals are listed in RCRA under F001 and F002. F001 specifies TCE and PERC used "in degreasing." F002 specifies TCE and PERC when they are spent and "all spent solvent mixtures/blends containing, before use, a total of ten percent or more (by volume) of one or more of the above halogenated solvents or those listed in F001, F004, or F005; and still bottoms from the recovery of these spent solvents and spent solvent mixtures." The

MSDSs discussed in the last section all contained TCE or PERC in concentrations of 10 percent or more. Thus the spent materials would make the waste streams hazardous waste.

This means that any waste stream from one of the alternative technologies that contains these materials from spotting chemicals is classified as hazardous waste simply because of the presence of TCE or PERC. This applies to sludge generated from spin-disk filters, still bottoms generated from distillation, separator water and the effluent from water-based technologies. Since spotting chemicals may be the origin of the PERC and TCE that appear in the waste streams, textile cleaning facilities should use alternatives that do not contain these materials.

Under RCRA, F003 specifies several other non-halogenated spent solvents including acetone, one of the ingredients used in the alternative spotting chemicals tested by IRTA. It includes "all spent solvent mixtures/blends containing, before use, only the above spent non-halogenated solvents; and all spent solvent mixtures/blends containing, before use, one or more of the above non-halogenated solvents, and, a total of 10 percent or more (by volume) of one or more of those solvents listed in F001, F002, F004, and F005; and still bottoms from the recovery of these spent solvents and spent solvent mixtures." IRTA used blends of acetone containing 10 percent acetone. To avoid having the waste streams from use of the alternative cleaning technologies classified as hazardous waste, commercial spotting chemical blends should contain no more than nine percent acetone.

TOXICITY OF SPOTTING AGENTS

As mentioned above, HESIS evaluated the MSDSs of some of the alternative spotting agents that were tested during this project. Today PERC and TCE are the POG spotting agents most widely used by cleaners, even those using alternative technologies for textile cleaning. PERC and TCE are both carcinogens. Several years ago, because PERC, the major dry cleaning agent, received negative publicity because it is a carcinogen, the suppliers and distributors converted away from the chemical in POG spotting agents. Although some of the POG spotting agents still contain PERC, the industry largely adopted TCE as an alternative. This was a poor choice since TCE is also a carcinogen and, unlike PERC, is classified as a VOC. It is not clear why the industry believed that TCE was a better choice than PERC.

Toxicity of PERC and TCE

PERC is a probable human carcinogen and several studies conducted recently link PERC exposure to leukemia and esophageal, bladder, colorectal and breast cancers. PERC exposure also can harm the digestive and nervous systems, blood, liver and urinary tract. Animal data also indicate that PERC can cause cancer and developmental damage.

Some occupational studies have shown that TCE produces central nervous system effects, as well as membrane, skin and gastrointestinal irritation and decreased appetite. Hepatotoxicity (liver cancer) has been associated primarily with TCE inhalation. Renal

failure has also been reported in concert with hepatic damage. Cardiac dysrhythmias may be induced by heavy TCE use in susceptible persons.

Toxicity of Alternative Spotting Agents

The alternative POG spotting agents evaluated during this project included two water-based cleaners, Cold Plus and Mirachem NP 2520. They also included Soy Gold 2500, acetone, DB, DPM and blends of these three materials.

The MSDSs for the two water-based cleaners indicate the materials contain no hazardous ingredients. Generally, water-based cleaners contain an appreciable amount of water. The toxicity of these two cleaners appears to be low.

The MSDS for Soy Gold 2500 indicates the material contains no hazardous ingredients. The soy cleaner is a fatty acid ester with added surfactants that make it water rinseable. HESIS indicates that, although there were no toxicity data on fatty acid esters in Toxnet, Scorecard and other chemical databases, they are not volatile, do not pose an inhalation hazard and are of low toxicity compared to organic solvents. The European Union, in conjunction with the U.S., is sponsoring research on vegetable oils and their fatty acid esters as substitutes for organic solvents in industrial processes.

Consistent with general solvent toxicity, overexposure to acetone affects the nervous system and causes skin and respiratory irritation. In the case of acetone, however, the threshold for producing these health effects is higher (the Permissible Exposure Limit or PEL of the acetone is 750 ppm) than for most other organic solvents. Thus, acetone is lower in toxicity than many other organic solvents.

The HESIS review indicates that ethylene based glycol ethers, including DB, can damage red blood cells and cause anemia. The propylene glycol ethers, including DPM, do not cause this problem and they are less volatile than the ethylene glycol ethers. However, they can produce neurotoxic effects through skin absorption as well as inhalation. As described earlier, IRTA stopped testing DB and, instead, used DPM part way through the project because DPM is lower in toxicity than DB.

V. SUMMARY AND CONCLUSIONS

The textile cleaning industry is undergoing a substantial change. The industry is converting away from PERC dry cleaning to a variety of solvent, carbon dioxide and water-based alternative processes. Cleaners rely heavily on spotting agents to remove the spots from garments before or after they are cleaned in the machines. Some of these materials, called POG spotting agents, are used for removing paint, oil and grease stains from garments. The major POG spotting agent used by cleaners contains TCE; other less widely used POG spotting agents contain PERC. Even many cleaners that have already converted to alternatives to PERC dry cleaning still use the POG spotting agents based on TCE and PERC.

PERC and TCE are carcinogens. They are classified as HAPs by EPA and TACs in California. Both solvents are listed on Proposition 65 and wastes from processes where PERC and TCE have been used for cleaning are classified as hazardous wastes. IRTA estimates that about 40,000 gallons per year of TCE is used in spotting chemicals and 150 gallons per year of PERC are used for that purpose.

There is a need to find effective POG spotting agents that could replace PERC and TCE. Although some POG spotting agents that do not contain PERC and TCE are on the market, cleaners have indicated that most do not work well. During this project, IRTA identified one new commercial product, Cold Plus, and developed several other materials that could be tested as safer alternatives. IRTA performed screening tests of several different types of cleaners to identify those that would be most effective. The screening tests were conducted on typical POG stains that were put on Goodwill garments made of a range of different fabrics. The screening tests helped IRTA to decide on which cleaning agents would be most effective to test in textile cleaning facilities.

The scaled-up testing was conducted at seven textile cleaning facilities that used a variety of PERC dry cleaning alternative technologies. The alternative spotting agents were tested for hydrocarbon, Green Earth, carbon dioxide and three water-based technologies. At each of the facilities, the spotting agents were tested on Goodwill garments and put through the machine. This was necessary to determine whether the spotting agent would leave a ring. In the proper spotting process, after the spotting agent is applied, it is rinsed with steam and dried with compressed air. IRTA deliberately selected alternatives that were water soluble or water rinseable. The results of the field tests indicated that none of the alternative spotting agents left a ring if spotting was performed properly. The spotting agents were then tested on each facility's garments. Those the spotters preferred were left for testing for one to five weeks. IRTA visited the facilities regularly to obtain feedback on whether the spotting agents were effective.

The spotters at the seven test facilities had personal preferences but all of the alternatives that were tested were judged to be effective by at least one of the facilities. Two water-based cleaners were tested and one of these is already a commercial product. Two glycol ethers, DB and DPM, were tested and found to be effective. One soy based cleaner was

tested and it performed well according to the spotters at some facilities. Various blends of soy, acetone, and the glycol ethers were also tested and judged to be effective. Because DB is a more toxic glycol ether than DPM, in the later testing, IRTA switched to this material. Table 5-1 shows the spotting agents that were successfully tested during the project.

Table 5-1
Alternative Spotting Agents That Performed Effectively

Spotting Agent	Type of Material
Cold Plus	Water-Based Cleaner
Mirachem NP 2520	Water-Based Cleaner
Soy Gold 2500	Methyl Ester and Surfactants
DPM	Glycol Ether
90% Soy Gold 2500/10% Acetone	Blend
90% Soy Gold 2500/10% DPM	Blend
90% DPM/10% Acetone	Blend

IRTA conducted a cost analysis which compared the cost of a TCE spotting agent with the cost of the alternative safer spotting agents. The results indicate that the cost of using the alternative spotting agents is lower than the cost of using TCE.

IRTA analyzed the regulations that affect spotting agents. When PERC and TCE from spotting agents are present in waste streams generated by textile cleaners, those streams are hazardous waste. Wastes from PERC dry cleaning alternative processes might not be considered to be hazardous wastes if PERC and TCE were not present. As a result, disposal of the wastes could be less costly. Both CARB and the local air districts in California may have jurisdiction over regulating the VOC and toxic content of spotting chemicals. The alternatives tested by IRTA were selected to have low VOC content and low toxicity.

HESIS assisted IRTA in evaluating the toxicity of the alternative spotting agents. The results of the analysis indicate that the alternative spotting agents tested during the project are lower in toxicity than PERC and TCE.

This project demonstrates that there are a variety of other safer materials that can be used in place of TCE and PERC spotting chemicals. These alternative materials were found to be effective for a variety of different textile cleaning processes. The alternatives are also less costly than TCE spotting chemicals used widely today.

Material Safety Data Sheet

Fast –PR

1. Identification of the Substance/Preparation and the Company/Undertaking

Substance or preparation trade name:	FAST – PR
Unique reference numbers(s):	052001
Company/undertaking name & address:	Caled Industries, 26 Hanes Drive, Wayne, NJ 07470
Telephone:	1-800-652-2533
Emergency telephone number:	1-800-424-9300 Chemtrec

2. Hazardous Ingredients

Substance:	Aprox. %	CAS #
Trichloroethylene	95	000079-01 50 ppm OSHA 8 HOUR TWA 200ppm OSHA 15 MIN STEL

3. Hazards Identification

Health: 2 **Flammability:** 1 **Reactivity:** 0

4. First aid measures

Skin contact:	Flush area with water. When irritation persists get medical attention.
Eyes contact:	Flush eyes with large amount of water. Get medical attention.
Inhalation:	Remove to fresh air. Get medical attention.
Ingestion:	Not normal route of entry. Give water and induce vomiting. Get medical attention.

5. Fire fighting measures

Suitable extinguishing media:	Water, dry chemicals
Unsuitable extinguishing media:	None known
Special hazards in fire:	Use protective clothing and self contained breathing apparatus.
Not	Consider flammable under normal use
Required special protective equipment for fire-fighters:	Wear Protective clothing and self contained breathing apparatus **in confined areas**

6. Accidental release measures

Personal precautions: Wear safety glosses and gloves
Environmental precautions: None known
Methods for cleaning: Flush area with water if locally permitted.
Dispose of in accordance with federal, state and local regulations.

7. Handling and storage

Handling: Keep container closed. Avoid contact with skin.

Storage: Keep container closed away from open flame, heat and sparks.

8. Exposure Controls

Engineering measures: Foam / Water / Fog
Control Parameters:
Personal protection equipment:
Eye protection: Safety glasses or safety shield. Eye wash station.
Hand protection: Neoprene gloves
Hygiene measures:

9. Physical and chemical properties

Appearance: clear to slightly hazy liquid
Odor: none
pH: 6.5-7.2
Boiling point: 1286-190
Melting point: F
Flashpoint: closed cup
Explosive properties:
Vapor pressure: 100
Relative density: 1.465
Solubility: insoluble

10. Stability and reactivity

Conditions to avoid: None known
Materials to avoid: water will lead to slow hydrolysis to form acid products.
Hazardous decomposition products: Hydrogen chloride and possible traces of phosgene.

Material Safety Data Sheet

Fast –PR

11. Toxicological information

Acute toxicity: -Local effects: - required at of application Excessive exposure may affect human health as follows:

Skin contact: May cause irritation and dermatitis.
Eye contact: Direct contact may cause irritation.
Inhalation: Mists may cause irritation to mucous linings.
Ingestion: Some as inhalation, including gastric disturbances.

12. Ecological information

None known

13. Disposal Considerations

Solvent can be reclaimed. Dispose of in Accordance With federal, state and local regulations.

14. Transport information

Classification data:

DOT: **Trichloroethylene CLS. 1Nu 1710, PG LII**
UN: CLS 6.1, UN 1710 ,PG III IMDG PAGE 6273

15. Regulatory information

Toxics Release Inventory SARA TITLE III, Section 313:
Trichloroethylene 200ppm OSHA 15 Min. STEL
50 ppm OSHA 8 hour TWA
Trichloroethylene is listed by SARA TITLE III Section 313 not regulated for water and ground transportation unless equal or exceeds 100lbs. per package. regulated for air transport per above dot info.

16. Other Information

Recommendations/restrictions:
Sources of key data used to compile:
NA= Not applicable ND= No data available NE= No establish <=Less than >= Greater than

We believe that the statements, Technical information and recommendation contained herein are reliable, but Without warrantee or guarantee of any kind, express or implied and we assume no responsibility for any loss, Damage, or expense, direct or consequential arising from their use.
This MSDS should be properly routed to all individuals who use or may come contact with this product, Understand and follow all pertinent employee and Community Right To Known Regulation.
Revision date: 01-04-07

MATERIAL SAFETY DATA SHEET

Date Issued: 11-05-2012

Picrin

1. PRODUCT AND COMPANY IDENTIFICATION

PRODUCT NAME: Picrin

GENERAL USE: For professional drycleaning use only.

PRODUCT DESCRIPTION: Stain Removal Agent

MANUFACTURER

R. R. Street & Co. Inc.
215 Shuman Boulevard/Suite 403
Naperville, IL 60563

Product Stewardship: 800-323-7206 (USA & Canada only) **or** 630-416-4244

24 HR. EMERGENCY TELEPHONE NUMBERS

Medical Emergency: 866-303-6947 (USA & Canada only) **or** 651-632-9272

Transportation Emergency: 800-424-9300 (USA & Canada only) **or** 703-527-3887

2. COMPOSITION / INFORMATION ON INGREDIENTS

Chemical Name	Wt.%	CAS#
Trichloroethylene	>75	79-01-6

3. HAZARDS IDENTIFICATION

POTENTIAL HEALTH EFFECTS

EYES: Substance may cause substantial eye irritation.

SKIN: May cause skin irritation. Prolonged or repeated contact may cause dermatitis.

SKIN ABSORPTION: Absorption through skin is possible but not a likely route of significant exposure.

INGESTION: Low to moderate toxicity.

Can cause adverse health effects as described under INHALATION. In the case of vomiting after ingestion, product may be aspirated into lungs causing chemical pneumonia, which in extreme cases could lead to death. See section 4, First Aid Measures, for more information.

INHALATION: High concentrations can cause central nervous system depression, irregular heartbeat, cardiac arrest, unconsciousness or death.

SIGNS AND SYMPTOMS OF OVEREXPOSURE

EYES: Irritation and pain.

SKIN: Irritation.

SKIN ABSORPTION: No data available.

INGESTION: Irritation of mouth, nausea.

INHALATION: Headache, nausea, dizziness, vertigo, fatigue, lightheadedness and coughing.

MEDICAL CONDITIONS AGGRAVATED: Skin contact may aggravate pre-existing dermatitis. Prolonged overexposure may complicate liver and kidney disease.

ROUTES OF ENTRY: Inhalation and skin.

4. FIRST AID MEASURES

EYES: Immediately flush eyes with plenty of water for at least 15 minutes. Get immediate medical attention.

SKIN: Remove contaminated clothing. Wash with soap and water. If irritation persists, call a physician.

INGESTION: Get immediate medical attention. Do not induce vomiting unless instructed to do so by poison center or physician.

INHALATION: Remove affected person to fresh air. If not breathing, give artificial respiration. Get immediate medical attention.

NOTES TO PHYSICIAN: Chlorinated hydrocarbons may sensitize the heart to epinephrine and adrenaline so that arrhythmias may occur.

ADDITIONAL INFORMATION: After emergency actions, call the emergency medical information number on page 1 or a physician immediately.

5. FIRE FIGHTING MEASURES

FLASHPOINT AND METHOD: None (TCC).

FLAMMABLE LIMITS: 8% to 45%

AUTOIGNITION TEMPERATURE: 420°C (788°F).

FLAMMABLE CLASS: Not applicable.

EXTINGUISHING MEDIA: Not applicable.

HAZARDOUS COMBUSTION PRODUCTS: Hydrogen chloride, phosgene.

OTHER CONSIDERATIONS: Concentrated vapor can be ignited by high-intensity ignition source.

FIRE FIGHTING EQUIPMENT: As in any fire, wear self-contained breathing apparatus pressure-demand, (MSHA/NIOSH approved or equivalent) and full protective gear.

6. ACCIDENTAL RELEASE MEASURES

SMALL SPILL: Clean up spill with absorbent material.

LARGE SPILL: Provide plenty of fresh air. Contain spill. Avoid breathing vapor. Clean up spills immediately with absorbent material, observing precautions in the Personal Protective Equipment section. Place absorbed material in closed containers for disposal (see section 13). Do not flush to sewer. Avoid contamination of ground and surface waters.

7. HANDLING AND STORAGE

GENERAL PROCEDURES: Not applicable.

HANDLING: Follow all MSDS/label precautions even after container is emptied because it may retain product residues.

STORAGE: Store in labeled, tightly sealed containers in a cool, dry, well ventilated area.

ELECTROSTATIC ACCUMULATION HAZARD: Not applicable.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

EXPOSURE GUIDELINES:

OSHA HAZARDOUS COMPONENTS (29 CFR 1910.1200)

		EXPOSURE LIMITS					
		OSHA PEL		ACGIH TLV		Supplier OEL	
		ppm	mg/m^3	ppm	mg/m^3	ppm	mg/m^3
Trichloroethylene	**TWA**	100		10[1]			
	STEL	200[2]		25			

TABLE FOOTNOTES:

1. A2: Suspected human carcinogen.

2. Ceiling concentration. A 300 ppm peak concentration is allowed for 5 minutes in any 2-hour period.

ENGINEERING CONTROLS: Local exhaust may be required to control vapor concentration.

PERSONAL PROTECTIVE EQUIPMENT

EYES AND FACE: Safety glasses with side shields, or goggles.

SKIN: Viton®, PVA, or Barrier™ gloves.

RESPIRATORY: NIOSH/MSHA approved air purifying respirator with an organic vapor cartridge or canister may be permissible under certain circumstances where airborne concentrations are expected to exceed exposure limits. Protection provided by air purifying respirators is limited. Use a positive pressure air supplied respirator if there is any potential for an uncontrolled release, exposure levels are not known, or any other circumstances where air purifying respirators may not provide adequate protection.

PROTECTIVE CLOTHING: Where contact is likely, wear the appropriate chemical resistant equipment, which depending on circumstances may include, chemical resistant gloves, a chemical suit, rubber boots, and chemical safety goggles plus a face shield.

WORK HYGIENIC PRACTICES: Wash thoroughly after handling. Do not smoke in presence of vapor. Do not eat or drink in work area.

OTHER USE PRECAUTIONS: Have eye wash station available. Do not wear contact lenses without eye protection.

9. PHYSICAL AND CHEMICAL PROPERTIES

PHYSICAL STATE: Liquid.

ODOR: Ethereal.

APPEARANCE: Clear.

COLOR: Colorless.

pH: Not applicable.

PERCENT VOLATILE: 100

VAPOR PRESSURE: 58 mm Hg at 20°C

VAPOR DENSITY: 4.5 (air = 1)

BOILING POINT: 87°C (188°F)

FREEZING POINT: -85°C (-121°F)

SOLUBILITY IN WATER: Negligible.

EVAPORATION RATE: 4.5 (butyl acetate = 1)

SPECIFIC GRAVITY: 1.45

VISCOSITY: No data available.

COEFF. OIL/WATER: 2.42

ODOR THRESHOLD: 20 ppm

10. STABILITY AND REACTIVITY

STABLE: Yes.

HAZARDOUS POLYMERIZATION: No.

CONDITIONS TO AVOID: Contact with open flame, electric arcs, other hot surfaces which can cause thermal decomposition.

HAZARDOUS DECOMPOSITION PRODUCTS: Hydrogen chloride, phosgene.

INCOMPATIBLE MATERIALS: Strong alkalies, oxidizers, sodium, potassium, lithium, aluminum, barium, magnesium, titanium.

11. TOXICOLOGICAL INFORMATION

ACUTE

DERMAL LD_{50}: >2,000 mg/kg (rabbit)

ORAL LD_{50}: >5000 mg/kg (rat)

INHALATION LC_{50}: 12,500 ppm (rat)

CHRONIC

TARGET ORGANS: Chronic overexposure to trichloroethylene has caused toxic effects in the liver, kidney, hearing, and central nervous system of experimental animals.

SENSITIZATION: Has produced allergic effects in laboratory animals.

CARCINOGENICITY

IARC: Trichloroethylene is classified as 2A (Probably carcinogenic to humans).

NTP: Trichloroethylene is on the NTP list of substances reasonably anticipated to be human carcinogens.

OSHA: Not listed as a carcinogen.

OTHER: ACGIH: A2. Limited epidemiology data have shown a weak association between trichloroethylene exposure and renal cancer.

OTHER: No data available.

REPRODUCTIVE EFFECTS: Not applicable.

MUTAGENICITY: Evidence for trichloroethylene is equivocal.

SYNERGISTIC MATERIALS: Alcohol.

GENERAL COMMENTS: Refer to Section 3 for additional information on potential health effects.

12. ECOLOGICAL INFORMATION

ENVIRONMENTAL DATA: Trichloroethylene has moderate persistence in the environment.

13. DISPOSAL CONSIDERATIONS

DISPOSAL METHOD: Recovered liquids may be sent to a licensed reclaimer or incineration facility. Contaminated material must be disposed of in a permitted waste management facility. Consult federal, state and local authorities for approved procedures.

EMPTY CONTAINER: Do not cut or weld empty drums.

RCRA/EPA WASTE INFORMATION: Contains material(s) listed by RCRA as a hazardous waste.

14. TRANSPORT INFORMATION

DOT (DEPARTMENT OF TRANSPORTATION)

PROPER SHIPPING NAME: Trichloroethylene

PRIMARY HAZARD CLASS/DIVISION: 6.1

UN/NA NUMBER: UN1710

PACKING GROUP: III

LABEL: Toxic, PG III

REPORTABLE QUANTITY (RQ) UNDER CERCLA: 8 gal

OTHER SHIPPING INFORMATION: Original 4x1-gallon packaging is approved for ground shipments only. Drums of this product contain a Reportable Quantity of trichloroethylene.

CANADA TRANSPORT OF DANGEROUS GOODS

PROPER SHIPPING NAME: Trichloroethylene

PRIMARY HAZARD CLASS/DIVISION: 6.1

UN/NA NUMBER: UN1710

PACKING GROUP: III

LABEL: Toxic

OTHER SHIPPING INFORMATION: Original 4x1-gallon packaging is approved for ground shipments only.

AIR (ICAO/IATA)

PROPER SHIPPING NAME: Trichloroethylene

PRIMARY HAZARD CLASS/DIVISION: 6.1

UN/NA NUMBER: UN1710

LABEL: Toxic

PACKING GROUP: III

PLACARDS: Consult applicable regulations governing air shipments.

IATA NOTE: Original 4x1-gallon packaging is not approved for air shipment. Consult applicable regulations for packaging requirements and quantity limitations.

15. REGULATORY INFORMATION

UNITED STATES

SARA TITLE III (SUPERFUND AMENDMENTS AND REAUTHORIZATION ACT)

311/312 HAZARD CATEGORIES:

FIRE: No. **PRESSURE GENERATING:** No. **REACTIVITY:** No. **ACUTE:** Yes. **CHRONIC:** Yes.

313 REPORTABLE INGREDIENTS: Trichloroethylene is reportable.

CERCLA (COMPREHENSIVE RESPONSE, COMPENSATION, AND LIABILITY ACT)

CERCLA RQ: Trichloroethylene has an RQ of 100 lbs.

REPORTABLE SPILL QUANTITY: 8 gals

RCRA STATUS: See section 13.

CANADA

WHMIS CLASS: Class D, Divisions 1 & 2

MEXICO

Regulated for transportation.

STATE REGULATIONS

MASSACHUSETTS

Contains one or more substances regulated by the Massachusetts Substance List.

CALIFORNIA

PROPOSITION 65 STATEMENT: Trichloroethylene is on the Proposition 65 list known to the State of California to cause cancer.

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16. OTHER INFORMATION

HMIS RATINGS	
HEALTH	3
FLAMMABILITY	1
REACTIVITY	0
PERSONAL PROTECTION	H

NFPA RATINGS