SUMMARY REPORT
OF THE EXTERNAL PEER REVIEW OF THE DRAFT TOXICOLOGICAL PROFILE FOR

1,2,3-, 1,2,4-, AND 1,3,5-TRICHLOROBENZENE

Submitted to:

The Agency for Toxic Substances and Disease Registry
Division of Toxicology
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October 2010

Printed on Recycled Paper

QUALITY NARRATIVE STATEMENT

ERG selected reviewers according to selection criteria provided by ATSDR. ATSDR confirmed that the scientific credentials of the reviewers proposed by ERG fulfilled ATSDR's selection criteria. Reviewers conducted the review according to a charge prepared by ATSDR and instructions prepared by ERG. ERG checked the reviewers' written comments to ensure that each reviewer had provided a substantial response to each charge question (or that the reviewer had indicated that any question[s] not responded to was outside the reviewer's area of expertise). Since this is an independent external review, ERG did not edit the reviewers' comments in any way, but rather transmitted them unaltered to ATSDR

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SECTION I

PEER REVIEWERS' SUMMARY COMMENTS

SUMMARY COMMENTS RECEIVED FROM

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Review of Draft Toxicological Profile for Trichlorobenzenes

General Comments

There may be reasons for modifying changing the internal organization of the chapters. I have only minor difficulties with the content of each section, but found the content awkwardly placed and unnecessarily repetitive. For example, the relatively exhaustive treatment of the toxicology data in the Summary of Health Effects within the section on Relevance to Public Health is much more exhaustive than necessary given the detailed descriptions of technical data in the Health Effects Chapter. In my view, the Relevance to Public Health chapter should contain clear and concise statements of judgments related to the probable public health impacts of exposures from the general and work environments as a way of bringing the bulletized treatment of the subject in the Public Health Assessment to a summary judgment of this information. The Public Health Assessment chapter rightly segregates sources of data as to being human or animal data. However, I believe it creates more concern about the absence of human data on a particular aspect of the toxicity data than is warranted. Somewhere there should be a statement that there is generally some substantial confidence that animal data is largely (if not always) predictive of adverse effects in humans and that confidence is increased when the animal data are extensive and of high quality and include consideration of likely human/animal differences based on experience with other related substances..

Charge questions:

Child's Health

Are there any data relevant to child health and development that have not been discussed in the profile and should be?

There are limited data (primarily a two-generation study and some less elaborate developmental studies) quoted that suggest that problems specific to child health and development is probably not an issue.

Are there any general issues relevant to child health that have not been discussed in the profile and should be?

Yes.

If you answer yes to either of the above questions, please provide any relevant references.

Data specific to postnatal development of the nervous system using more sophisticated measures than employed in traditional two-generation studies have not been done.

Chapter 1. Public Health Assessment

Does the chapter present the important information in a non-technical style suitable for the average citizen? If not suggest alternate wording.

Generally the chapter does provide summarized categorical information in a way that the general public should be able to understand. My major concern is the one identified in the general comments. The atomization of this information stands in the way of relating the magnitude of exposures that humans encounter and developing a clear statement of judgment of whether these exposures are likely to lead to adverse effects on health. In my view the section of Relevance to Public Health should focus on this message rather than the details of the toxicological data.

I also believe that there is too sharp a distinction between "no data in humans" vs. an adequate database in animals that are generally relied on to allow judgments to be made. The public needs to realize that animal data is generally where dependable data are available for making these judgments as reliable human data are generally not available for most chemicals.

I have concern with the statement that trichlorobenzene could be the product of the metabolism of other compounds. If this is true (and it seems odd), examples of chemicals that could give rise to the trichlorobenzenes should be identified in this section. I further note that this statement is made elsewhere in the document and the reader is referred to section 6.5 for data on this subject. There are no examples provided in section 6.5. Therefore, I doubt such data exist based on my simple understanding of the chemistry. I cannot conceive of a precursor that would be metabolized to trichlorobenzenes. There may be ways of producing trichlorophenols in vivo, but trichlorobenzenes would be virtually impossible to imagine.

In section 1.6, I question whether the use of the word babies for the offspring of animals is likely to be understood. The term "pups" is usually technically applied to rats, I think that pups would be more intuitively and universally understood by the lay public than "babies". The use of babies is anthropomorphic and will be misunderstood by some because it is simply incorrect.

Do the answers to questions posed in major headings adequately address the concerns of the lay public? Are these summary statements consistent, and are they supported by the technical discussions in the remainder of the text? Please note sections that are weak and suggest ways to improve them.

Logically, the questions used would seem to be questions that the general public would have interest in. I would strongly suggest that this question be addressed in a research project aimed at determining how effective these answers are. Asking a technical person whether a lay person would be satisfied by these answers is not all that appropriate.

I can say that most of the answers appear to accurately reflect the concern. However, some of the answers that build obvious barriers to the public's understanding of the role of animal experimentation in health and safety assessments should be reconsidered. If a chemical will enter or leave the body of an animal (at least another mammal) by a given route, it is pretty improbable that it would not enter or leave a human body, for example.

I do believe that provision of regulatory standards for the trichlorobenzenes is important as is the section that provides other sources of information is good.

Are scientific terms used that are too technical or that require additional explanation? Please note such terms and suggest alternate wording.

Some note is made of overly technical terms that were used in Chapter 2 below.

Chapter 2. Relevance to Public Health

Do you agree with those effects known to occur in humans as reported in the text? If not, provide a copy of additional references you would cite and indicate where (in the text) those references should be included.

Generally, the effects that occur in humans are well identified. However, I am concerned that this section of the document contains obscure terminology (e.g. massive hemaoptysis [p. 10], anisokaryosis [p. 11]) as well as a number of more commonly used, but not necessarily understood, technical terms describing adverse health effects in humans. This language could easily be simplified and connect more clearly with the information provided in Chapter 1.

Are the effects only observed in animals likely to be of concern in humans? Why or why not? If you do not agree, please explain.

The applicability of animal data to health concerns in humans is difficult to deal with in the context of the relevance to public health without reference to the information provided in the next chapter. I would suggest that the order of the two chapters be reversed with the Health Effects Chapter preceding the chapter dealing with Relevance to Public Health. It is very difficult to put the various effects that are observed into context without the discussions in the health effects section. Therefore, it is premature to begin discussing these results in Chapter 2. Two examples are discussed, hepatic effects that are observed in animals would be expected to occur in humans at comparable doses. The more likely problem is that humans may develop liver damage due to immune system reactions, so animal results are more likely to be false negatives. On the other hand, the renal effects in male rats that are secondary to accumulation of the α-2u-globulin are very unlikely to occur in humans. Therefore, the write-up in Chapter 2 amounts to a

bad summary without substantive support. An additional awkwardness of Chapter 2 is that this is where MRLs are developed which seem to demand some experimental detail to explain points of departure, etc. The incorporation of the experimental detail in Chapter 2 almost guarantees that it will be understood by the lay person, if they even read it. In other words, the sequence is extremely awkward and inefficient. I strongly suggest that the order of Chapters 2 and 3 be reversed and all of the detail of toxicological studies (whether human or experimental animal) be provided in the chapter now labeled as Health Effects.

Alternatively, the toxicological details could be left out of Chapter 2 so that it is clear that it is more of an overview of judgments that can be made with the available data. In this arrangement, the MRLs could be cited, but their derivation should follow the Health Effects Chapter.

In addition to difficulties for the lay reader, this chapter, as structured, is difficult to address by technical readers. It provides relatively detailed assessment of the studies that are available, but no citations are incorporated. As a result it is difficult to tie this discussion in with discussion of studies in the Health Effects Chapter. A technical reader is much better off going directly to the latter chapter (i.e. read the document backwards) to avoid getting mired down in what appears to be a technical review, but with no citations and geniune discussion of the nature of the data. However, structured, introductory language in the document could more prominently direct the reader to chapters that are appropriate to their interests and expertise.

Have exposure conditions been adequately described? If you do not agree, please explain.

Conversely to the answer to the prior question, the exposure conditions should be kept with the current Chapter 2 (but potentially made Chapter 3) as it is the combination of exposure and quantitative health effects data with respect to dose that allows the development of MRLs. In whatever order presented, the exposure information must be coupled to the MRL development.

The MRLs for non-carcinogenic endpoints are presented in this chapter (although modeling is presented in an appendix where there were adequate data). The appropriate studies were selected for benchmark dose modeling and the treatment of the data to arrive at MRLs for different durations of exposure appear to apply conventional assumptions to derive the equivalent of an RfD or ADI for each interval.

On the other hand, the handling of the carcinogenicity data was not well explained (pages 23-24). There are clear evidence of treatment-related hepatic carcinomas in mice. The renal pathology in male rats would usually be expected to produce renal tumors, but deficiencies in that study probably prevented their appearance. If they did arise, however, they could be dismissed as being male-specific response.

The rationale for dismissing the hepatic carcinomas in mice is simply that the doses for both the neoplastic and non-neoplastic changes occurred at higher doses. This is not a compelling argument. There needs to be a clearer explanation of this departure in the section where the MRLs are developed.

Chapter 3. Health Effects

Comment on odd language or conclusions:

Occasionally the terminology used in this and the following chapters appears awkward or odd. In addition statements are made that are non-sequiturs. A list is provided with a page number where this happens.

A general point is that dietary or drinking water concentrations appear to be routinely converted to doses in mg/kg/day. It is occasionally indicated that authors estimates were used, but it is frequently not clear if the mg/kg/day doses were calculated based on actual food and water consumption or were they estimates based on general consumption figures? If it is the latter, assumptions used in making these conversions should be clearly stated along with the description of the study being discussed. **Most important, it should be stated which conversion is being made in each case discussed.** Otherwise NOAELs and LOAELs in the original publication and the document are very difficult to reconcile with one another.

p. 47. What is meant by "individualization of hepatocytes"?

p. 47 and other places in document. Standard deviations do not ”render” anything. Rather it is the variability observed in the study that resulted in a determination that the observations were not statistically significant. In other words, while there is a difference observed with treatment, but objective evaluation of the data, using statistical principals indicates that the differences may be due to chance rather than treatment.

p. 46, ocular effects. The Gage study reports lacrimation and with exposure to 1,2,4-trichlorobenzene. This is inappropriately refuted by lack of gross or macroscopic lesions in the document. Lacrimation does not lead to such lesions, in fact, it probably prevents the development of such lesions. The lacrimation is reflecting the fact that irritation is occurring and is real despite lack of overt pathology.

p. 48. It cannot be assumed that other endocrine organs were examined just because adrenals were reported upon. The adrenal gland used to be frequently examined for evidence of stress. This study was reported in 1983, well before concerns of endocrine disruption erupted. Therefore, this conclusion is pure speculation.

p. 49. It is not clear to me that lack of effect on electrolyte levels provides assurance that there are no metabolic effects. I would label this section, Electrolyte Balance OR simply say that no metabolic effects have been observed (or there is no data pertaining to Metabolic Effects). More important, there needs to be a definition of what is constitutes a metabolic effect. In various parts of the document it appears to refer to effects on xenobiotic metabolism, electrolyte balance, whereas it probably should refer to interference with intermediary metabolism. It would be best to utilize these more specific terms rather than catchall, rather meaningless phrase such as metabolic effects.

p. 51. The statement that there were no data identified related to developmental effects or cancer is not consistent with reports of a two-generation study (by the oral route) on p. 18 or the description of hepatocellular carcinomas in mice (also administered orally)(p. 23-24). At least there should be some reference to the appropriate section where the oral route is discussed. If they are real outcomes by that route, it is likely they will be produced with inhalation, it is just that there are no specific data obtained through inhalation. It is odd that the oral two-generation study was not mentioned in the section on Reproductive Effects for the same reason. In all likelihood this would not be a route specific effect, either. In the next section labeled Death, a developmental study by Kitchin and Ebron is identified that does use the inhalation route.

p. 69. The statement about relative doses of trichlorobenzene to affect mice (to induce cancer and non-neoplastic effects) do not appear to be supported by the figure on this page. The differences in the NOAELs for hepatic damage in rats and mice are trivial.

p. 65, third to last line. The description of doses is confusing. 14.6 mg/kg/day was administered to male rats, who was given the 52.5 mg/kg dose?

p. 87, first para. of endocrine effects. Black et al administered trichlorobenzene to pregnant females. Were both pups and dams examined for histopathology? Not clear.

p. 88. The differences are as likely to be due to different pathologists as they are differences in rat strains. The threshold for reporting subtle effects varies widely among pathologists. That is the reason NTP convenes pathology working groups. The CMA study was not subjected to such a review.

p. 113. 1,2,3-trichlorobenzene, last sentence. Sentence would make more sense if it said "These results are also consistent with as much as 95% of the ..... The data provided do not "imply" anything about how the material measured in feces got there. The two options presented are simply boundary conditions. Same comment applies in the discussion of 1,3,5-trichlorobenzene on p. 116.

p. 115. It is stated that trichlorobenzenes can be produced by metabolism of other compounds. This section does not identify specific compounds of which trichlorobenzenes could be metabolites, but refers to Section 6.5. There is no information in section 6.5 on this issue.

Toxicity – Quality of Human Studies

Were adequately designed human studies identified in the text?

Yes, to the extent they exist. The "studies" available in humans do not provide useful data for the profile.

Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the profile?

Yes

Were all appropriate NOAELs and/or LOAELS identified for each study? Would other statistical test have been more appropriate? Were statistical test results of study data evaluated properly?

There were not any clear NOAELs or LOAELs in the human data.

Are you aware of other studies which may be important in evaluating the toxicity of the substance?

No

Toxicity – Quality of Animal Studies

Were adequately designed animal studies identified in the text?

Yes

Were the animal species appropriate for the most significant toxicological endpoint of the study?

This is a difficult question. It is generally assumed that animal data, particularly in mammals, is appropriate for identifying hazards in humans unless there are clear data to the contrary. In the present document, the male rat is clearly not a good model for human renal damage risk because the response has the hallmarks of an effect that is specific to the male rat.

Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the text?

I had insufficient time to check each and every study cited to confirm this is true. I suggest this is the job of an editor rather than a technical reviewer.

Were all appropriate NOAELs and LOAELs identified for each study? Were all appropriate toxicological effects identified for the studies?

Addressing this question is made impossible by the organization of the document. However, I have confirmed that appropriate NOAELs and LOAELs have been identified for critical studies.

If appropriate, is there a discussion of the toxicities of various forms of the substance?

This is not an issue for the trichlorobenzenes as long as the different isomers are being considered separately as they are in this document. However, there are so few data available on isomers other than the 1,2,4-isomer, it has to be stated that effects of the other two isomers are simply not well characterized. This conclusion is consistent with those of the document.

Were the appropriate statistical tests used in the interpretation of the studies? If not, which statistical tests would have been more appropriate? Were statistical test results of study data evaluated properly?

In the primary reports, particularly those which are unpublished, statistical analyses of results were not critically considered. Most of these studies date from the 1980s when consideration of statistical evaluation was frequently not rigorous. In some cases, the methods of statistical analysis were not even provided. Comments have been made to this effect in the short reviews of unpublished studies at the end of this review.

Are you aware of other studies that may be important in evaluating the toxicity of the substance? If you are citing a new reference, please provide a copy and indicate where (in the text) it should be included.

No. However, I should note that the short turnaround on this review precluded my usual literature search to determine if all the data have been included. In large part this was due to short notice, but was complicated by mishipment of the document. As a consequence, I have to assume the literature search was thorough and all relevant data were included to have a prayer of meeting the deadline.

Levels of Significant Exposure (LSE) Tables and Figures

Are the LSE tables and figures complete and self-explanatory? Does the "Users Guide"explain clearly how to use them? Are exposure levels (units, dose) accurately presented for the route of exposure?

The LSE tables are clear. The figures are not. I was not able to locate a definition of what the numbers represented in the designation of significant exposures. To be specific what does the number in O1k, 02r, ... mean? Both the symbol and the letter are defined in the footnote, but the number is not as best I could tell.

Do you agree with the categorization of "less serious"for the effects cited in the LSE tables?

This categorization is appropriate, but the depiction in the hepatic column does not indicate whether a higher dose (>100 ppm) would lead to more serious liver damage. Is it a gradation in type of lesion or could it be reflecting dose-response? This is a general comment about the definition of less serious; it is not aimed at specific interpretation of the trichlorobenzene data.

If MRLs have been derived, are the values justifiable? If no MRLs have been derived, do you agree that the data do not support such a derivation?

Yes, but this was done in Chapter 2, not Chapter 3. Very confusing.

Evaluation of Text

Have the major limitations of the studies been adequately and accurately discussed?

The major limitations of the studies are identified, but not adequately discussed. Most important is a more scientific discussion of why the carcinogenicity data are not being used in the development of MRLs. I do not disagree with the conclusions, but the reasons for coming to those conclusions were not sufficiently developed. As a consequence, the rationale for ignoring these data are not compelling.

The discussion of the hematological effects suffers from the same problem. If a decrement in hemoglobin or hematocrit of $\geq$ 10% is treatment-related it is a significant effect that will physiological consequences in some individuals (i.e. being within the normal range is not an adequate argument for dismissing). What if there was an individual with an hemoglobin of 10 or a hematocrit of 30? Would not a 10% decrement in that individual be considered harmful? A more appropriate argument is that these are not critical effects as they occur at much higher doses than those of studies used in the development of MRLs.

Has the effect, or key endpoint, been critically evaluated for its relevance in both humans and animals?

I cannot say there was a "critical" evaluation. Clearly, judgments were made, but in some cases (as outlined above) without substantive justification.

Have "bottom-line" statements have been made regarding the relevance of the endpoint for human health?

In general, the document does drive towards bottom-line conclusions, where they can be appropriately made. Note previous comments related to mouse liver tumors resulting from 1,2,4-trichlorobenzene treatment as an exception to this.

Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provide and other data provided to you but not presented in the text.

In general, I agree with the document's conclusions about critical effects and support the MRLs that were derived.

Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.

Yes.

Has the animal data been used to draw support for any known human effects? If so, critique the validity of the support.

There were no "known" human effects that could be tied to a meaningful dose-response relationship.

Section 3.3. Genotoxicity

The conclusions in this section appear appropriate. However, there was no obvious used of these data to support interpretations of the mouse liver tumor data.

Section 3.4 Toxicokinetics

Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance?

There is adequate discussion of these issues.

Have the major organs, tissues, etc. in which the substance is stored been identified?

Not really. All tissue data depends upon measurement of radioactive tags. Identifications of the chemical forms in tissues were not made in any species by any route. In other words, these data do not exist and substantive conclusions cannot be made about deposition of the trichlorobenzenes in various tissues.

Have all applicable metabolic parameters been presented? Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented?

No, all applicable metabolic parameters have not been presented. However, this appears to be due to a lack of data rather than an error on the part of the authors of this document.

Is there adequate discussion of the differences in toxicokinetics between humans and animals?

There are rudimentary discussions of uptake, distribution and elimination of the radioactive label. Thus, there are only very rudimentary toxicokinetic data.

Is there an adquate discussion of the relevance of animal toxicokinetic information for humans?

There is some discussion of interspecies differences in the metabolism of the trichlorobenzenes. The major differences are in type and level of conjugations. None of this data was human data.

If applicable, is there a discussion of the toxicokinetics of different forms of the substance?

Differences in metabolism of the three trichlorobenzenes were discussed, but are limited to information outlined in answer to the prior question. Therefore, conclusions are not possible in this area.

Section 3.5 Mechanisms of Action

The discussion of pharmacokinetic mechanisms (section 3.5.1) is a waste of paper. There are not sufficient data to speak meaningfully to this point. The same comment can be leveled at section 3.4.5. There are insufficient data to make discussion of these issues useful

The discussion of changes in drug metabolism enzymes in this section is probably more relevant to mechanisms of toxicity than pharmacokinetics, especially the induction of ALA synthetase. As indicated, this result has implications for the induction with porphyria. There are no data provided that indicate that changes in P450 or glucuronyltransferase have substantive effects on the pharmacokinetics of the trichlorobenzenes. While this is consistent with the concluding sentence in the section, one wonders what purpose is served by this section.

Section 3.6 Toxicities Mediated through the Neuroendocrine Axis

Nothing substantive to report.

Section 3.7. Children's Susceptibility

As concluded by the document, the available data do not indicate a higher susceptibility of children. However, there really have been no studies of subtle effects on postnatal development (i.e. studies have largely been limited to dosing during pregnancy and sophisticated measures of postnatal development have not been applied).

Section 3.8. Biomarkers of Exposure and Effect.

Other than measures of the trichlorobenzenes or their metabolites in blood or urine, no biomarkers have been identified. While trichlorobenzene exposure will certainly give rise to these chemicals in the body, there have been no studies that would establish their use as measures of exposure (i.e. how the amounts of these materials in blood or tissues relate to an external dose, both in magnitude and over time).

Section 3.9. Interactions with Other Chemicals

There are very limited data in this area. Most of the discussed interactions are very unlikely to occur at less than monumental exposures.

Section 3.10. Populations that are Unusually Susceptible

No useful information

Section 3.11. Methods for Reducing Toxic Effects

The suggestion of reducing systemic glutathione concentrations is a very dangerous intervention. I suggest that this not be included in the document. Somebody might get the idea this is a benign intervention.

Section 3.12. Adequacy of the Database

It is unlikely that all the data needs identified in this section will be addressed with new data. Conducting many of the identified studies would be a waste of time considering what is already known about these compounds. Rather than producing this laundry list, it would be more useful to identify data needs that could be critical. Frankly, with the frequency and magnitude of exposures that are likely, I cannot identify any research needs that are truly critical.

The information in Section 6 is much better organized and to the point of important data gaps.

Chapter 4. Chemical and Physical Information

No comment.

Chapter 5. Production, Import/Export, Use and Disposal

No comment.

Chapter 6. Potential for Human Exposure.
(Check bullets for section)

No comment. The data presented speak for themselves.

Chapter 7. Analytical Methods

No comment.

Chapter 8. Regulations and Advisories

Important section. No comment.

Chapter 9. References

No comment.

Unpublished Studies of Applicable to Review

Provide comment for each unpublished study included in the profile

Dow, 1956. Simply a compilation of range-finding toxicological data on 1,2,3-trichlorobenzene. Methods not described, so data cannot be viewed with high confidence.

DuPont, 1971. Study of acute oral LD_{50}, subacute oral toxicity, and subacute inhalation toxicity. Definition of subacute toxicity is not general clear. In this case, the oral study was conducted for three days, but it seems a longer treatment was intended. Inhalation study involved treatment for 12 days. Studies appear competently conducted. Pathological findings were reported in summary fashion. Subacute studies utilized repeated administration at a single dose level. Text indicates congestion of the lungs and marked centrilobular necrosis of the liver of one of six rats. No effects were noted in the subacute inhalation study. This study is of limited value.

Ethyl Corp 1975. A test of 1,2,4-trichlorobenzene in Salmonella and Yeast. Methods described, but result were not discussed. Data appear negative by usual criteria applied to these systems.

Jorgenson et al. 1976. A range finding study of short-term studies of 1,3,5-trichlorobenzene among other two other chemicals. Testing consists of single dose oral toxicity, primary skin irritation, eye irritation, skin sensitization, in vitro mutagenesis, and 60 min inhalation studies. The studies were competently conducted, but actual exposure conditions in the inhalation study could not be defined by measurement (i.e. estimated from amount generated). The study is old and the utility of the data may be limited as protocols have changed in the meantime. Using these data for estimation of risk should be kept within the bounds of the protocols used (i.e. not extrapolated to other conditions). The data do not seem to have been subject to formal statistical analysis.

Dow, 1981 Simply a compilation of chemicals detected in workplace sampling. All the information related to adverse effects are references to standard sources with little or no description of how these figures were derived.

Shimada et al. 1983. The methodology described is standard. However, none of the actual data were presented. It appears that trichlorobenzene was negative in the DNA repair assay, but positive in the ARL/transformation assay (i.e. growth in soft agar). No statistical analyses were described.

CMA, 1989. This 13 week dietary study of 1,2,4-trichlorobenzene appears to be competently done. Losses due to volatilization were compensated for by increasing the nominal concentration. The amounts present were confirmed by measurement. Doses were estimated from food consumption data. The data were presented in a clear way. Pathology was reported by experimental group and dose-response information is easily extracted. The only major difficulty is that the statistical analyses were described in an Appendix that was not included in the package.

Hiles, 1989. This was a CMA sponsored 13-week study in mice. Comments on CMA 1989 apply here as well. This report does more explicitly describe loss of test compound to volatilization. It also provides a good description of statistical methods that were probably also used in the other study, but in which the appendix describing statistical methods was missing. The results of pathology data was clearly discussed with respect to dose. The major deficiency of the study is the wide separation between the low dose (220 ppm) and the intermediate dose (3850 ppm). Therefore, there is not a good gauge of where the actual NOAEL occurs.

SUMMARY COMMENTS RECEIVED FROM

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Overview

The draft profile provided a good overview of the potential exposures and health effects from Trichlorobenzene at all life stages. Where data were available the discussion of the potential effects of Trichlorobenzene on offspring after exposure of parents or from exposure to the fetus after maternal exposure has been discussed. The appropriate rodent and cell culture models (*in vitro)* have also been discussed. This profile on Trichlorobenzene also provided the appropriate succinct interpretations of the key literature and was in keeping with the ATSDR profile format making for an easy to read document. No new literature is suggested for inclusion. The author(s) did a very good job is capturing the appropriate and pertinent literature on Trichlorobenzene for this profile. This is a well written and complete document.

Other Comments

Page xi under peer review – please change my affiliation to read

James E Klaunig, PhD, Professor and Chair, Department of Environmental Health, School of Public Health Indiana University at Bloomington , Bloomington, Indiana

CHAPTER 1. PUBLIC HEALTH STATEMENT

This chapter adequately addresses the overview of the potential health effects and possible exposure to Trichlorobenzene. It is written in a high school reading level and adequately prepares the lay public with the background of the potential health effects of Trichlorobenzene. The tone of the chapter was factual and was suitable for understanding by the average US citizen. No other wording is suggested. This section adequately addresses concerns that the lay public would have regarding Trichlorobenzene exposure and possible health effects No additional information is suggested to be included.

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

This chapter does an adequate job in evaluating the available toxicity data on Trichlorobenzene and the significance of this information on human health. The document addresses the known effects of Trichlorobenzene on humans and on animals. The summary of effects is well done and no additional references, that I am aware of, exist for inclusion in this text. The potential effects of Trichlorobenzene are discussed and the concerns to humans from exposure are

adequately addressed. The exposure conditions have been adequately described. One concern is the lack of references to the primary literature in this section. Is this done on purpose or an oversight? References to the literature on which the statements are based should be included Pages 9-13). If the references are not included then referral to the section of the document where this information will be found should be included. No additional information is suggested to be added nor changes to this section of the document.

CHAPTER 3. HEALTH EFFECTS

DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

This section is well written and contains the necessary information on the specific health effects of Trichlorobenzene in Humans and in animals. The Human data was presented before animal data. The issue of dose response was adequately addressed in the document. The toxicological effects are organized according to route of exposure. The levels of significant exposure (LSE) tables were adequately presented. The quality of the human studies identified in the text was adequately addresses and the limitations of each study were noted in the text. The conclusions drawn by the authors of the studies were appropriate and accurately reflected in this section No suggested changes are offered. The NOAELs and/or LOAELs were identified for each study and appeared to be appropriately cited and noted in the text. The statistical tests used in the studies appeared appropriate and no suggestions for alternative statistics are suggested by this reviewer. I am unaware of any additional studies that may be important in evaluating the toxicity of Trichlorobenzene. I am unaware of any additional data relevant to child health and developmental effects that have not been discussed in the profile or other general issues relevant to child health that have not been discussed in the profile

The animal studies reported in the literature were adequately noted and reported in the text of this document. Animal study design was commented on in the text and appeared to be appropriate. The conclusions drawn by the document authors appeared appropriate, accurate, and were justified. The appropriate NOAELs and LOAELs were identified for each study. All of the appropriate toxicological effects appeared to be identified for Trichlorobenzene. The statistical tests used in the interpretation of the animal studies were appropriate. No additional information is suggested to be included. I am unaware of any additional data relevant to child health and

developmental effects that have not been discussed in the profile or other general issues relevant to child health that have not been discussed in the profile.

Levels of Significant Exposure (LSE) Tables and Figures

The LSE tables and figures appear to be complete and self-explanatory. Although, as with other ATSDR profile documents that I have examined and reviewed, these tables are overwhelming and difficult to readily evaluate (in part because of the multiple pages they frequently occupy). This is not a reflection of the writing of this particular document but a reflection of the voluminous data that is needed to populate these tables.

I have no suggestions on how to improve the readability of these tables however. The categorization of less serious or serious for Trichlorobenzene is adequate based on the guidelines for this document, although as a reviewer, I have trouble with this simplistic categorization for a complex issue.

The limitations of the studies on Trichlorobenzene have been adequately and accurately addressed. The key effects and key endpoints have been addressed in both humans and animals. The relevance of the data on human health and health effects have been adequately noted in the text and the conclusion are appropriated for the data set available on Trichlorobenzene. Where data were available the dose-response relationships for the endpoints noted were adequately referenced and noted. No additional information is suggested to be included.

TOXICOKINETICS

There is adequate discussion of absorption, distribution, metabolism, and excretion of Trichlorobenzene (where data are present). The applicable metabolic parameters been presented for Trichlorobenzene and there is discussion of the differences in toxicokinetics between humans and animals and relevance of animal toxicokinetic information for humans. No additional information is suggested to be included. I am unaware of any additional data relevant to child health and developmental effects that have not been discussed in the profile or other general issues relevant to child health that have not been discussed in the profile

MECHANISMS OF ACTION

The mechanism of liver toxicity (the major toxic target) has not been fully elucidated. This is reflected in the review and has been adequately addressed. No additional information is suggested to be included. This data gaps on this information are further expanded in the data needs section. I am unaware of any additional data relevant to child health and developmental effects that have not been discussed in the profile or other general issues relevant to child health that have not been discussed in the profile

TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

This has been addressed and the conclusions that Trichlorobenzene is not mediated through this mechanism are correct. No additional information is suggested to be included. I am unaware of any additional data relevant to child health and developmental effects that have not been discussed in the profile or other general issues relevant to child health that have not been discussed in the profile

CHILDREN'S SUSCEPTIBILITY

This section has been appropriated written and children susceptibility addressed correctly. No additional information is suggested to be included.

BIOMARKERS OF EXPOSURE AND EFFECT

This section correctly and adequately addressed the issue of biomarkers (or the lack there of, except for measuring the material) for Trichlorobenzene. No additional information is suggested to be included.

INTERACTIONS WITH OTHER CHEMICALS

The discussion of the interactive effects with other substances has been addressed and cited correctly. No additional information is suggested to be included.

POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Based on the available limited data especially the lack of mechanistic data the conclusions reached in this section are correct. No additional information is suggested to be included. I am unaware of any additional data relevant to child health and developmental effects that have not

been discussed in the profile or other general issues relevant to child health that have not been discussed in the profile

METHODS FOR REDUCING TOXIC EFFECTS

Since there is limited information about the mechanism of action of Trichlorobenzene, limited data exist on this topic. The text was adequate in addressing this topic. No additional information is suggested to be included.

ADEQUACY OF THE DATABASE

This section was well done and addressed the data gaps and needs to fully access the topics noted above. The inclusion of the graphs/tables indicating data – existing information was useful as an illustration for the further needs. No additional information is suggested to be included.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

This chapter is adequately written and the topic well addressed. No additional information is suggested to be included.

CHAPTER 5. PRODUCTION, IMPORT ,EXPORT, USE, AND DISPOSAL

This chapter provides an adequate overview of the topic for Trichlorobenzene. No additional information is suggested to be included.

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

This chapter has adequately addressed the information available on the environmental fate and potential for human exposure to Trichlorobenzene. The text was sufficient and technically sound. The text describes the sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures. No additional information is suggested to be included. I am unaware of any additional data relevant to child health and developmental effects that have not been discussed in the profile or other general issues relevant to child health that have not been discussed in the profile

CHAPTER 7. ANALYTICAL METHODS

This chapter is appropriate. No additional information is suggested to be included.

CHAPTER 8. REGULATIONS AND ADVISORIES

This chapter is appropriately presented. No additional information is suggested to be included.

REFERENCES

The references appear to be complete. No additional information is suggested to be included.

SUMMARY COMMENTS RECEIVED FROM

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Peer Review of ATSDR's Toxicological Profile of 1,2,3-, 1,2,4-, and 1,3,5-Trichlorobenzene

CHAPTER 1. PUBLIC HEALTH STATEMENT

Chapter 1 is well-written, and presents the important information in a non-technical style suitable for the average citizen. I believe that the chapter adequately addresses the concerns of the lay public, although I do have a few changes to recommend. In the second paragraph on page 1, it is stated: "Although the total number of NPL sites evaluated for these substances is not known,…". Would it be possible to provide a brief explanation of why that is the case? Without additional explanation, a lay person might get the impression that the EPA coordinates the evaluation of hazardous waste sites for the presence of trichlorobenzenes, but doesn't keep a good record of the sites that are evaluated. In Section 1.4 on page 3, the last entry at the bottom of the page seems contradictory: "Studies in animals suggest that trichlorobenzenes do not accumulate in the body, but accumulate in fish." I suggest that this sentence be rephrased. In Section 1.7 on page 5, I suggest adding avoidance of an extremely high consumption of root crops and fish as a method for reducing the risk of exposure.

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

The draft profile document states that the general population is exposed to trichlorobenzenes through inhalation of ambient air and ingestion of food and drinking water, with the oral route likely the most important, and that occupational exposure may occur through inhalation and dermal exposure where trichlorobenzenes are produced or used. I believe that potential human exposure conditions have been adequately described. I agree that there is very limited information regarding health effects in humans following exposure to trichlorobenzenes and that the available information is inadequate to determine a clear target for trichlorobenzenes in humans. However, I agree that certain adverse effects observed in animal studies, particularly liver effects in rats, may be relevant to humans and may be of concern. I believe that Chapter 2 would be strengthened considerably if the discussion and justification presented in Section 3.5.3, Animal-to-Human Extrapolations, were included at the end of Section 2.2. Regarding minimal risk levels (MRLs), I agree that there are insufficient data to set MRLs for the inhalation route for any of the three trichlorobenzene isomers, and insufficient data to set MRLs for the oral route for 1,2,3- and 1,3,5-trichlorobenzene. However, sufficient data on liver effects in rats were identified for setting Intermediate-Duration and Chronic-Duration MRLs for oral exposure to 1,2,4-tricholorbenzene. The profile document states that appropriate methodology does not exist for setting MRLs for the dermal

route of exposure. I have annotated some suggested language in certain places in the chapter to add clarification to the reasoning for excluding studies.

CHAPTER 3. HEALTH EFFECTS

Section 3.1 INTRODUCTION

Section 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

3.2.1 Inhalation Exposure

Toxicity – Quality of Human Studies

The profile document states that there is very limited information on exposure to trichlorobenzenes and possible associated health effects in humans. I agree that the extremely limited data presented are inadequate for determining levels of significant exposure (LSEs) or MRLs. I am not aware of any human studies that may be important in evaluating the toxicity of the trichlorobenzenes.

Toxicity – Quality of Animal Studies

No inhalation studies on 1,2,3-trichlorobenzene were identified. While a few inhalation studies on 1,2,4- and 1,3,5-trichlorobenzend were identified and discussed, no study was deemed adequate for setting MRLs for any exposure duration. I believe that the studies have been appropriately characterized and that conclusions drawn by the authors of the studies are accurately reflected in the text. I am not aware of any other studies that may be important.

Levels of Significant Exposure (LSE) Tables and Figures

The NOAELs listed in Tables 3-1 and 3-2 for 1,2,4- and 1,3,5-trichlorobenzene, respectively, are 100 ppm and 130 ppm. These are NOAELs for histological effects in tissues and organs. An effect such as increased relative liver weight in the absence of an accompanying histological effect was not considered relevant (for setting an MRL). These NOAELs are a bit unusual, in that they represent the highest doses tested in the respective studies. Ordinarily, a NOAEL is identified in a study that shows toxicity at one or more dose levels. Limitations in the studies mentioned in Chapter 2 (lack of quantitative data, inadequate animal numbers) were said to preclude their being used to set MRLs. I believe the profile document ought to state somewhere that the actual NOAELs in these studies could actually be higher (if higher doses were tested) or could possibly be lower (if more animals were used), and that this is why they are unsuitable for setting MRLs, even though they are included in the LSE tables.

Evaluation of Text

I am persuaded by the arguments provided in the profile document (mainly in Chapter 2) regarding inadequacies or lack of relevance of the data for setting inhalation MRLs. But, I think it is confusing to have a discussion of the studies and inclusion of NOAELs in Tables 3-1 and 3-2 without additional explanatory text in this section as to why they are unsuitable for setting inhalation MRLs.

3.2.2 Oral Exposure

Toxicity – Quality of Human Studies

The profile document states that there is very limited information on exposure to trichlorobenzenes and possible associated health effects in humans. I agree that the extremely limited data presented are inadequate for determining levels of significant exposure (LSEs) or MRLs. I am not aware of any human studies that may be important in evaluating the toxicity of the trichlorobenzenes.

Toxicity – Quality of Animal Studies

Although several oral animal studies were identified for 1,2,3- and 1,3,5-trichlorobenzene, none was deemed adequate for setting MRLs. In some cases, NOAELs were established and reported in Tables 3-4 and 3-5. Some of these reported "NOAELs" were actually the highest dose tested, and thus cannot be characterized according to the usual definition of a NOAEL, as discussed above. Inadequacies were identified in all cases that precluded using these studies to set MRLs. In come cases there was inadequate quantitation to allow assessment of possible dose-response relationships for histological changes, while in others there were non-histological effects seen at lower doses (e.g., increased relative kidney weights) that were not accompanied by histological changes in tissues and organs. The text appears to accurately reflect the conclusions drawn by the authors of the studies. I am not aware of other studies that might be important.

There were many more studies available for 1,2,4-trichlorobenzene than for the other two isomers. Adequate studies of 1,2,4-trichlorobenzene were identified for setting intermediate-duration and chronic-duration MRLs, based on dose-responses for hepatocellular hypertrophy in male rats. All relevant studies are adequately described in the profile document and NOAELs and LOAELs are presented in Table 3-3. Reasons for disqualifying certain studies for setting MRLs are given, including studies of acute duration that are inadequate for setting an acute-duration MRL. I have annotated some suggested language in certain places (mostly in Chapter 2) to add clarification to the reasoning for excluding studies. The text

appears to accurately reflect the conclusions drawn by the authors of the studies. I am not aware of other studies that might be important.

Levels of Significant Exposure (LSE) Tables and Figures

The LSE tables are complete and self-explanatory, except that a little more explanation may be needed for the NOAELs which do not follow the conventional toxicological definition. The categorizations of "less serious" and "serious" seem appropriate. No studies of 1,2,3- or 1,3,5-trichlorobenzene were considered adequate for setting MRLs of any duration. Intermediate-exposure and chronic-exposure MRLs for 1,2,4-trichlorobenzene were derived using benchmark dose (BMD) modeling. The modeling is adequately described, including the choice of the benchmark response (BMR) (Chapter 2).

Evaluation of Text

The arguments provided in the profile document (in both Chapters 2 and 3) for including or excluding studies (or certain data from studies) are generally clear and accurate. The profile document pays adequate attention to dose-response relationships. The endpoint ultimately chosen for deriving both intermediate-exposure and chronic-exposure MRLs, hepatocellular hypertrophy in male rats, had good dose-response information for BMD modeling. As indicated above, liver effects in rats may be relevant to humans in light of the limited metabolism information on 1,2,4-trichlorobenzene from human liver cell preparations. I believe that the key endpoint has been critically evaluated for its relevance to humans.

3.2.3 Dermal Exposure

Toxicity – Quality of Human Studies

No human studies of dermal exposures to trichlorobenzenes were located.

Toxicity – Quality of Animal Studies

A few dermal-exposure studies were located for all three isomers (Tables 3-6, 3-7, 3-8). The studies were done mostly in rabbits and most were studies of 1,2,4-trichlorobenzene. No serious effects were observed for either 1,2,3- or 1,3,5-trichlorobenzene, but a few serious effects were reported for 1,2,4-trichlorobenzene. The studies of 1,2,3- and 1,3,5-trichlorobenzene were single exposures, but there was one 7-day study in the former. The studies of 1,2,4-trichlorobenzene were mostly of several weeks' duration. The lone chronic study was done on 1,2,4-trichlorobenzene; it was considered of insufficient quality for assessing carcinogenic potential.

Levels of Significant Exposure (LSE) Tables and Figures

The LSE tables are complete as far as reflecting available data. But, they are somewhat sparse considering the paucity of data on dermal exposure. There are no figures because figures do not accompany tables in profile documents for dermal studies. No MRLs have been derived because appropriate methodology does not exist for deriving dermal MRLs.

Evaluation of Text

Effects have been reported and conclusions stated, but not necessarily regarding the relevance to human health. Where applicable, limitations of studies have been adequately described.

Section 3.3 GENOTOXICITY

Section 3.4 TOXICOKINETICS

No studies are available describing the absorption, distribution, metabolism, and elimination (ADME) of 1,2,3-, 1,2,4- or 1,3,5-trichlorobenzene following oral, inhalation, or dermal exposure in humans. Only oral studies in animals are available.

There is adequate discussion of ADME for the available studies. The organs and tissues in which the substance is stored have been identified for oral studies in various animal species for 1,2,3-, 1,2,4- and 1,3,5-trichlorobenzene. There is a statement in Section 3.4.5 (page 125) that if PBPK models for trichlorobenzenes exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations. I did not see such a discussion. I don't know if that means that no such models exist, or if it means that the text containing such discussion has inadvertently been left out. I did not see a discussion for any of the three isomers of the differences in toxicokinetics between humans and animals, or of the relevance of animal toxicokinetic information for humans.

Section 3.5 MECHANISMS OF ACTION

According to the profile document, the toxicity of trichlorobenzenes does not appear to be route-dependent and the liver appears to be the main target organ in animals regardless of the duration of exposure. The mechanism(s) of liver toxicity induced by trichlorobenzenes has not been elucidated, but it is said probably to involve arene oxide intermediates which form during the initial transformation to trichlorophenols. The document states that because there is virtually no information on health effects of trichlorobenzenes in humans, the animal species that is the most appropriate model for human exposure is not known, but the rat appears most sensitive. Based on limited information on the metabolism of 1,2,4-

trichlorobenzene by microsomal preparations from human livers and information from effects of other chlorinated benzenes in humans, the document states that it is reasonable to assume that excessive exposure to trichlorobenzenes could induce liver effects such as porphyria in humans. This conclusion seems reasonable.

Section 3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Section 3.7 CHILDREN'S SUSCEPTIBILITY

I do not know of any data relevant to child health and development effects or any general issues relevant to child health that have not been discussed in the profile and should be.

NOTE: The instructions for Section 3.7 in the "Guidelines for peer review of ATSDR's Toxicological Profiles" are misplaced. They appear at the end of the general instructions just before the instructions for Chapter 1 instead of at Section 3.7.

Section 3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Although trichlorobenzenes have been detected in blood, adipose tissue and exhaled breath, the profile document states that their presence cannot be used as specific biomarkers of exposure to trichlorobenzenes because they can also be generated from metabolism of higher chlorinated benzenes. This is a logical conclusion.

The document states that no specific biomarker of effect can be identified in humans because there is such limited information. The statement for animals is different. The document states that it is difficult to envision a health condition that could be attributed solely to exposure to trichlorobenzenes. I think it would be better to simply make the same statement for animals that is made for humans, and not engage in speculation.

Section 3.9 INTERACTIONS WITH OTHER CHEMICALS

The document states that no studies were located regarding interactions among trichlorobenzenes or between trichlorobenzenes and other chemicals. However, it goes on to give examples of what it terms inhibitory types of interactions of 1,2,4-trichlorobenzene with several pesticides. This appears to be an inconsistency that needs to be cleared up. There is no discussion of interactive effects that might occur at hazardous waste sites.

Section 3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

The document identifies individuals with compromised liver function as a potentially susceptible subpopulation. This is based on the assumption that, although a specific target of trichlorobenzene toxicity in humans has not been identified, the liver could be a main target based on studies in animals. This seems reasonable.

Section 3.11 METHODS FOR REDUCING TOXIC EFFECTS

3.11.1 Reducing Peak Absorption Following Exposure

The management and treatment are general for the class of trichlorobenzenes. No controversies or hazards to unusually susceptible individuals were identified.

3.11.2 Reducing Body Burden

No information was located for reducing body burden of trichlorobenzenes.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The only possible method mentioned for mitigating the effects of trichlorobenzenes was reducing glutathione levels to prevent, at least in part, the effects of 1,2,4-trichlorobenzene. No controversies or special hazards were mentioned.

Section 3.12 ADEQUACY OF THE DATABASE

3.12.1 Existing Information on Health Effects of Trichlorobenzenes

3.12.2 Identification of Data Needs

The data needs are presented in a neutral, non-judgmental fashion. The text adequately justifies why further development of identified data needs would be desirable, and why additional studies to fill some existing data gaps do not seem necessary.

3.12.3 Ongoing Studies

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

I am not aware of any information or values that are wrong or missing in the chemical and physical properties tables.

CHAPTER 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

I am not aware of any information that is missing or wrong.

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

The text has appropriately traced trichlorobenzenes from their point of release to the environment until they reach the receptor population. Sufficient and technically sound information regarding the extent of occurrence at National Priority List (NPL) sites is provided. The text covers pertinent information relative to transport, partitioning, transformation, and degradation of the trichlorobenzenes in all media. Information is provided on levels monitored or estimated in the environment using proper units for each medium. The information includes the form of the substance measured. There is adequate discussion of the quality of the information.

The text describes sources and pathways of exposure for the general population and for individuals working in occupations involved in the manufacture and/or use of trichlorobenzenes. Subpopulations of the general population with potentially high exposures are identified. The text states that the general population is exposed to trichlorobenzenes from inhalation of ambient air and ingestion of food and water, suggesting that the most important human intake routes are ingestion of root crops, fish, and drinking water. Subpopulations identified to have potentially high exposures to trichlorobenzenes include individuals residing in heavily industrialized areas or near superfund sites, and individuals who consume large amounts of fish and root crops. These pathways of exposure to trichlorobenzenes and these subpopulations with potentially higher exposures are logical and reasonable. The identified data needs seem reasonable.

CHAPTER 7. ANALYTICAL METHODS

The chapter is complete with regard to existing analytical methods pertinent to the trichlorobenzenes. No data/method needs are identified.

CHAPTER 8. REGULATIONS AND ADVISORIES

I have annotated a needed change in the fourth paragraph on page 197 where it is erroneously stated that the chronic-duration oral MRL set by ATSDR for 1,2,4-trichlorobenzene was derived using BMD modeling of incidence data for diffuse fatty change in female rats. I am not aware of other regulations or guidelines that may be appropriate for Table 8-1.

CHAPTER 9. REFERENCES

I do not know of additional references that ought to be included.

UNPUBLISHED STUDIES

Dow Chemical (1956): Range-finding study for 1,2,4-trichlorobenzene.

This was a very limited range-finding study in rats and rabbits. There is not enough information to enable evaluation of the adequacy of the design and methodology. Sample sizes were either very small or not identified. There is no way to ascertain potential confounding factors from the information given. The authors' conclusions for eye and skin contact studies in rabbits seem appropriate based on the limited data. But, it's hard to determine if the conclusion of low acute oral toxicity is warranted, because there were only two dose groups each having only two subjects, and at the higher dose one of the two animals died.

CMA (1989): Three-month dietary range-finding study for 1,2,4-trichlorobenzene in rats.

This was a well-designed study with 10 rats/sex/dose at 0, 200, 600, and 1800 ppm. Good methodology was documented and there were no apparent inadequacies or confounding factors. The conclusion of a significant effect of 1,2,4-trichlorobenzene on mean liver, kidney and testis weights appears valid, as well as the conclusion of microscopic treatment-related alterations in the kidney and liver of high-dose males and in the liver of high-dose females.

Dow Chemical (1981): Industrial hygiene survey of 1,2,3-, 1,2,4-trichlorobenzene, and other chemicals.

This was a comprehensive industrial hygiene survey in the Organic Chemicals Product Development Distribution Center and Warehouse at Dow. The design, methodology and reporting appear to be adequate. The conclusion that all measured 8-hour time-weighted-average exposures were within acceptable guidelines appears to be valid.

Shimada et al. (1983): Study of effects of 1,2,4-trichlorobenzene and other chemicals on cultured liver cells.

The design, methodology and reporting appear adequate. No study inadequacies or confounding factors were apparent. The conclusion that the chlorobenzenes (including 1,2,4-trichlorobenzene) induced transformations in ARL cells but were not genotoxic to hepatocytes seems valid.

Hiles (1989): 13-week range-finding study in mice.

This was a well-designed study with 10 mice/sex/dose at 0, 220, 3850, and 7700 ppm. Good methodology was documented and there were no apparent inadequacies or confounding factors. The conclusion that liver-weight changes and microscopic liver changes were treatment related appears to be valid.

Ethyl Corp (1975): *In vitro* microbiological mutagenicity study of 1,2,4-trichlorobenzene and other ethyl compounds.

The assay appeared adequate in design, methodology and reporting. There were no apparent confounding factors. The conclusion that 1,2,4-trichlorobenzene was not mutagenic in the assay appears valid.

DuPont (1982): Comparative toxicity study of ODCB and 1,2,4-trichlorobenzene.

The acute oral, subacute oral and subacute inhalation toxicity studies were somewhat limited in terms of the number of doses and the number of rats tested. The stated conclusion that these experiments indicated the ODCB and 1,2,4-trichlorobenzene had roughly equivalent toxicity was qualified by a statement that more detailed experiments would be needed to differentiate more decisively. I agree that more detailed experiments would be needed. A single four-hour exposure of rats to 1,2,4-trichlorobenzene by inhalation showed no lethality. A primary skin irritation and sensitization test of 1,2,4-trichlorobenzene in guinea pigs showed a greater degree of irritation in older animals than younger ones, but did not appear to cause sensitization. The design and methodology of the guinea pig study appeared to be adequate and the conclusions valid.

Jorgenson et al. (1976): Toxicity studies of 1,3,5-trichlorobenzene and other chemicals.

Skin irritation and eye irritation studies in rabbits showed 1,3,5-trichlorobenzene to be mildly irritating. A skin sensitization study in guinea pigs, an inhalation study in rats, and *in vitro* mutagenicity tests were all negative. The oral study was an LD_{50} study in rats and mice. The *in vivo* experiments appeared to have adequate numbers of doses and numbers of animals per dose. The methodology of all tests appeared adequate. The authors' conclusions appear valid.

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SECTION II

ADDITIONAL REFERENCES AND DATA SUBMITTED BY THE PEER REVIEWERS

There were no additional references and data submitted by reviewers for this review.

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SECTION III

ANNOTATED PAGES FROM THE DRAFT PROFILE DOCUMENT

ANNOTATED PAGES FROM
THE DRAFT PROFILE DOCUMENT
SUBMITTED BY

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In the other developmental study in rats, pregnant animals were administered 0, 36, 120, or 360 mg/kg/day 1,2,4-trichlorobenzene on Gd 9–13 and were sacrificed on Gd 14 (Kitchin and Ebron 1983). Rats that received the highest dose, 360 mg/kg/day, lost weight and had moderate hepatocellular hypertrophy (only the liver was examined microscopically); the no-observed-adverse-effect level (NOAEL) for these effects was 120 mg/kg/day. While doses of 360 mg/kg/day did not increase resorptions or cause significant embryolethality or teratogenicity, they significantly retarded fetal development as measured by reduced head length, crown-rump length, somite number, and protein content. These end points were evaluated only in dams administered 360 mg/kg/day 1,2,4-trichlorobenzene and controls, but not in groups dosed with 36 or 120 mg/kg/day 1,2,4-trichlorobenzene, which makes this study inadequate for MRL derivation, because the NOAEL for weight loss and liver effects (120 mg/kg/dg) may not be the NOAEL for retarded fetal development.

In the developmental studies in mice, pregnant mice were administered 0 or 130 mg/kg 1,2,4-trichlorobenzene on Gd 8–12 (Chernoff and Kavlock 1983; Gray and Kavlock 1984; Gray et al. 1986). This treatment did not significantly affect offspring viability, reactive locomotor activity of the pups evaluated at various times up to 200 days of age, or reproductive performance of the offspring to produce a second generation. The use of only one dose level in these studies precludes constructing dose-response relationships for the end points measured. The lack of reported effects also precludes using this study for MRL derivation.

Rimington and Ziegler (1963) reported increased liver microsomal enzyme activities, increased urinary excretion of porphyrins, and also elevated levels of porphyrins in the liver of rats following daily gavage doses of 500 mg/kg/day for 10 days. The limited scope and single dose level precludes considering this study for MRL derivation. Carlson and Tardiff (1976) administered 1,2,4-trichlorobenzene in doses of 0, 10, 20, or 40 mg/kg/day to male rats by gavage in corn oil for 14 days. Sacrifices were conducted on day 15, and liver microsomal enzymes were analyzed. Blood was also collected for hemoglobin and hematocrit determinations. Sections of the liver were also prepared for histological examination. Administration of 1,2,4-trichlorobenzene resulted in dose-related increases in cytochrome c reductase, cytochrome P-450, glucuronyltransferase, EPN detoxification, and azoreductase. 1,2,4-Trichlorobenzene induced a dose-related increase in relative liver weight (all doses, 15% at the lowest dose, 28% at the highest dose). There were no significant effects on hemoglobin concentration or hematocrit. No specific information regarding liver histopathology was provided. Because the Carlson and Tardiff (1976) study is of limited scope and provided no information regarding histology of the liver, it is considered inadequate for MRL derivation.

Intermediate-Duration MRL

- An MRL of 0.1 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to 1,2,4-trichlorobenzene.

No relevant intermediate-duration studies in humans were located. The intermediate-duration oral database for 1,2,4-trichlorobenzene consists of two 3-month dietary studies in rats (CMA 1989; Côté et al. 1988), a 13-week dietary study in mice (Hiles 1989), two studies in rats aimed mainly at evaluating porphyrin metabolism and enzyme induction in the liver by 1,2,4-trichlorobenzene (Carlson and Tardiff 1976; Rimington and Ziegler 1963), and a multi-generation reproductive study in rats (Robinson et al. 1981). As a whole, these studies suggested that the liver and kidneys are targets for 1,2,4-trichlorobenzene and that male rats may be more sensitive than females. Administration of 730 mg/kg/day 1,2,4-trichlorobenzene (only dose level tested) by gavage to male albino rats caused intense necrosis and fatty change in the liver (only organ examined) and increased urinary porphyrins (Rimington and Ziegler 1963). Treatment of male albino rats via the diet with a much smaller dose, 40 mg/kg/day, increased relative liver weight (9–14%) and induced microsomal enzymes, but did not induce histological alterations in the liver (Carlson and Tardiff 1976).

In the multi-generation study, doses of up to 33 mg/kg/day in males and 54 mg/kg/day in females (mean doses estimated by the investigators consumed by 83 days of age F0 generation of rats) did not affect fertility in the F0 or F1 generation or affect the time of vaginal opening in F2 females (Robinson et al. 1981). Treatment with 1,2,4-trichlorobenzene did not affect neonates' weight, litter size, or viability during the pre-weaning period in any generation. Post-weaning growth of F1 rats was not affected by 1,2,4-trichlorobenzene. Tests for locomotor activity in the F1 or F2 generation rats were unremarkable. Of the organs weighed in the study (which included the liver and kidneys), only the adrenals were affected by 1,2,4-trichlorobenzene. Absolute weight of the adrenals of F0 and F1 males and females were significantly increased relative to controls (11–12% in F0 and 4–6% in F1); no histological evaluation of the glands was conducted. No histological damage was found in the livers and kidneys. Results from blood chemistry tests in F0 and F1 rats did not reveal any treatment-related alterations. The significance of the increase in adrenals weight is unknown. EPA (IRIS 2010) states that a 1-month study was performed by the Agency in which five rats/group were dosed by gavage with 53 mg/kg/day 1,2,4-trichlorobenzene in corn oil. Microscopic examination of the adrenals from treated rats showed moderate vacuolization of the zona fasciculata; the control group showed only slight vacuolization. A 14% increase in absolute adrenal gland weight and a 13% increase in relative adrenal weight were found. According to EPA (IRIS 2010, last revised 11/01/96), this study indicated that the increase in adrenal gland weight observed by Robinson et al. (1981) could be associated with vacuolization of the zona fasciculata. Since these observations are not supported by results from an acute-duration study (Black et

2. RELEVANCE TO PUBLIC HEALTH

Both the 14-week study in rats by CMA (1989) and the 13-week study in mice by Hiles (1989) evaluated a comprehensive number of end points and presented the results in a manner useful for establishing dose-response relationships, and can potentially be used for MRL derivation.

Data sets of centrilobular hepatocyte hypertrophy in male rats and relative liver weights in male and female rats (CMA 1989), as well as hepatocyte atrophy and degeneration in male mice (Hiles 1989) were analyzed using the benchmark dose (BMD) approach for MRL derivation. Data for renal effects in male rats were not considered for modeling due to the strong suggestive evidence that this may be a unique response of the male and not relevant for quantitative risk assessment (EPA 1991). Specific indications that this may be the case include the increased incidences of hyaline droplets, granular casts, and tubule dilation, and the fact that none of these lesions occurred in female rats. In addition, since there is not enough evidence to dissociate the interstitial nephritis from the male-specific nephropathy, interstitial nephritis was also not considered for modeling. In support of this position is the fact that interstitial nephritis did not occur in female rats.

Models in the EPA Benchmark Software (BMDS version 2.1) were fit to the data sets for centrilobular hepatocyte hypertrophy in male rats and relative liver weights in male and female rats from the CMA (1989) study, as well as hepatocyte atrophy and degeneration in male mice from the Hiles (1989) study. A benchmark response (BMR) of 10% was selected in the absence of data that would support a lower BMR. In accordance with EPA (2000) guidance, BMDs and the lower-bound confidence limits on the BMDs (BMDLs) associated with an extra risk of 10% are calculated for all models. For continuous data, in the absence of a clear criteria as to what level of change in organ weight should be considered adverse, the BMR was defined as a change in mean body weight gain equal to 1 standard deviation from the control mean (EPA 2000). Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) is chosen. None of the models could provide an adequate fit for relative liver weight in female rats. A summary of the modeling results is presented in Table 2-1.

Although Table 2-1 shows that the $BMDL_{1SD}$ of 9.41 mg/kg/day would be a slightly more protective point of departure for MRL derivation than the $BMDL_{10}$ of 14.35 mg/kg/day for hepatocyte hypertrophy in

male rats, the latter is preferred as the point of departure on the basis of being a more biologically meaningful end point. The MRL is derived by dividing the $BMDL_{10}$ of 14.35 mg/kg/day for centrilobular hepatocyte hypertrophy by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability). This yields an intermediate-duration oral MRL of 0.1 mg/kg/day for 1,2,4-trichlorobenzene. Detailed information regarding the modeling of hepatocyte hypertrophy in male rats is presented in Appendix A. Note that rounding to ~~the nearest~~ one decimal place would give the same MRL if based on relative liver weight

Chronic-Duration MRL

- An MRL of 0.1 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to 1,2,4-trichlorobenzene.

No relevant chronic data in humans exposed orally to 1,2,4-trichlorobenzene were located, but there are 104-week dietary bioassays in rats (Moore 1994a) and in mice (Moore 1994b). In the study in rats, groups of Fisher-344 rats (50/sex/group) were fed a diet containing 0, 100, 350, or 1,200 ppm 1,2,4-trichlorobenzene for 104 weeks. The diet provided doses of 0, 5.6, 19.4, or 66.5 mg/kg/day 1,2,4-trichlorobenzene to males and 0, 6.9, 23.5, or 81.4 mg/kg/day 1,2,4-trichlorobenzene to females. Parameters evaluated included mortality (twice daily), clinical signs, body weight and food consumption (weekly for 16 weeks and every 4 weeks thereafter), hematology (week 52 and 78 for cellular morphology and leukocyte differential, from control and high-dose groups), organ weight (at termination, brain, brainstem, liver, kidneys, testes, and epididymis), and gross necropsy and histological examination of all major organs and tissues at termination. Treatment with 1,2,4-trichlorobenzene resulted in a significant reduction in survival rate in males dosed with 66.5 mg/kg/day. Survival rate in the control, 5.6, 19.4, and 66.5 mg/kg/day males at week 104 were 84, 80, 84, and 60% respectively. There were no distinct or pronounced compound-related differences in clinical signs between treated and control groups. Differences in body weight between treated and control rats were <10% throughout the study. Food consumption was decreased 4–7% in treated groups relative to controls during the study. The only statistically significant hematology findings were a decrease in basophiles at week 52 and monocytes at week 105 in males dosed with 66.5 mg/kg/day, which the investigators considered minor. No evidence of leukemia was noted. Gross necropsy at termination showed increased incidence of liver and kidney abnormalities in males dosed with 19.4 and 66.5 mg/kg/day and a slight increase in incidence of uterine masses in treated females relative to controls; these changes were not discussed any further. Significant changes in organ weight were limited to an increase in absolute and relative liver weight in both male and female rats receiving the highest doses of 1,2,4-trichlorobenzene and a decrease in absolute and relative testes weight in males dosed with 5.6 and 19.4 mg/kg/day. Treatment-related histological alterations were restricted to the liver of males and females and to the kidneys of males and consisted of the following: hepatocellular hypertrophy, focal cystic degeneration, diffuse fatty change, transitional renal

cell hyperplasia, and increased severity of chronic rat nephropathy in males. Incidences of liver lesions are presented in Table 2-2 (note that a smaller number of animals from the low-dose groups were examined for histopathology).

The incidences of transitional cell hyperplasia in the kidneys of male rats were as follows: 2/50, 0/19, 2/50, and 34/50 in males dosed with 0, 5.6, 19.4, and 66.5 mg/kg/day 1,2,4-trichlorobenzene, respectively. Since there is strong evidence from the 14-week study (CMA 1989) suggesting that the renal lesions in male rats may represent a male-specific response not relevant for MRL derivation and that renal cell hyperplasia reported in the 104-week study is a typical response seen in the male rat nephropathy, renal cell hyperplasia is not considered any further as a potential end point for MRL derivation.

In the study in mice, groups of B6C3F$_1$ mice (50/sex/group) were fed a diet containing 0, 150, 700, or 3,200 ppm 1,2,4-trichlorobenzene for 104 weeks (Moore 1994b). The diet provided doses of 0, 21, 100.6, or 519.9 mg/kg/day 1,2,4-trichlorobenzene to males and 0, 26.3, 127, or 572.6 mg/kg/day 1,2,4-trichlorobenzene to females. End points monitored were the same as in the study in rats described above (Moore 1994a). The liver was the target for 1,2,4-trichlorobenzene in mice. The most significant effect was an increase incidence of hepatocellular carcinoma in mid- and high-dose mice (8/50, 5/50, 27/50, and 50/50 in males and 1/50, 1/50, 28/50, and 46/50 in females). Centrilobular hepatocytomegaly was also significantly increased in mid- and high-dose males (0/50, 0/50, 27/50, and 20/50). Since non-neoplastic effects were observed only at higher doses than in rats and carcinoma occurred at that same dose level, this study will not be considered any further for MRL derivation.

Table 2-2 shows that: (1) diffuse fatty change was significantly increased in males and females only at the highest dose; (2) focal cystic degeneration occurred at lower incidence in the low- and mid-dose males compared to controls, and was significantly increased only at the highest dose; (3) hepatocellular hypertrophy in female rats occurred at increased frequency only at the highest dose; and (4) only hepatocellular hypertrophy in male rats exhibited dose-response characteristics. Based on these facts, only the hepatocellular hypertrophy in male rats was considered for MRL derivation.

Models in the EPA Benchmark Software (BMDS version 2.1) were fit to the data set for hepatocellular hypertrophy in the liver of male rats. A BMR of 10% was selected in the absence of data that would support a lower BMR. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an

maternal tissues renders this study inadequate for MRL derivation because of the inability to inspect dose-response relationships.

Intermediate-Duration MRL. No intermediate-duration oral MRL was derived for 1,2,3-trichlorobenzene. No relevant human data were located. Only one intermediate-duration study was available for this compound (Côté et al. 1988). In that study, groups of Sprague-Dawley rats (10/sex/group) were fed a diet containing 0, 1, 10, 100, or 1,000 ppm 1,2,3-trichlorobenzene for 13 weeks. This diet provided doses of 0, 0.08, 0.78, 7.6, 78 mg/kg/day 12,3-trichlorobenzene to males and 0, 0.13, 1.3, 12, or 113 mg/kg/day to females. End points evaluated included body weight (weekly), food consumption (weeks 1, 4, 8, 12), urinalysis (weeks 4, 8, 12), and clinical signs (daily). At termination, the rats were necropsied and blood was collected for hematological and clinical chemistry testing. Hepatic microsomal aniline hydroxylase (AH), aminopyrine demethylase (APDM) activities, and liver protein content were also determined. Bone marrow from the femur was aspirated for cytological evaluation. All major tissues and organs were prepared for microscopic examination. There were no treatment-related deaths. Food consumption was not affected; body weight gain from high-dose males was reduced 10.2% relative to controls (only data for males shown). There were no significant alterations in hematology or clinical chemistry parameters, and urinalyses were unremarkable. No significant gross changes in tissues were reported. Statistically significant changes in organs weight were limited to increases in relative liver weight (14%) in males dosed with 78 mg/kg/day and in relative kidney weight in males dosed with 0.08 mg/kg/day (14%), 0.78 mg/kg/day (14%), and 78 mg/kg/day (21%). 1,2,3-Trichlorobenzene had no significant effect on the hepatic mixed function oxidase activities measured. For the most part, compound-related histopathology was reported as mild and was limited to the liver and thyroid of generally high-dose rats and appeared to be more severe in males. However, the investigators provided only a qualitative description of the histological examinations; incidences of lesions were not presented. In the liver, most treated groups showed mild-to-moderate increases in cytoplasmic volume and anisokaryosis of hepatocytes, mostly in perivenous and midzone areas. High-dose rats showed mild aggregated basophilia as well as mild widespread midzonal vacuolization due to fatty infiltration. Changes in the thyroid consisted of reduction in follicular size, increased epithelial height from flattened cuboidal cells to columnar shape, and reduced colloid density. Changes in the high-dose group varied from mild to moderate. The urinalyses were unremarkable. Since no dose-responses can be constructed with the histological data, this study is considered inadequate for use as basis for MRL derivation. and since the increases in relative kidney weights in males were not accompanied by any histological changes

Chronic-Duration MRL. No chronic-duration oral data in humans or in animals were located for 1,2,3-trichlorobenzene. Therefore, a chronic-duration oral MRL was not derived for this compound.

82 mg/kg/day for males and 0, 0.13, 1.5, 17, and 146 mg/kg/day for females. End points evaluated included body weight (weekly), food consumption (weeks 1, 4, 8, 12), urinalysis (weeks 4, 8, 12), and clinical signs (daily). At termination, the rats were necropsied and blood was collected for hematological and clinical chemistry testing. Hepatic microsomal AH, APDM activities, and liver protein content were also determined. Bone marrow from the femur was aspirated for cytological evaluation. All major tissues and organs were prepared for microscopic examination. Gross observations did not reveal any significant treatment-related alterations. Significant changes in organs weight were limited to an increase in relative liver weight in males dosed with 82 mg/kg/day (11%), an increase in absolute kidney weight in males dosed with 0.81 and 7.7 mg/kg/day (~20%), and increases in relative kidney weight in males dosed with 0.81 (14%), 7.7 (25%), and 82 mg/kg/day (14%). There were no significant alterations in hematology or clinical chemistry parameters. 1,3,5-Trichlorobenzene had no significant effect on AH and APDM activities. For the most part, compound-related histopathology was mild and was limited to the liver, thyroid, and kidneys, generally high-dose rats, and appeared to be more severe in males. However, the investigators only provided a qualitative description of the histological changes; incidences of lesions were not presented. In the liver, most treated groups showed mild-to-moderate increase in cytoplasmic volume and anisokaryosis of hepatocytes mostly in perivenous and midzone areas. High-dose rats showed aggregated basophilia as well as widespread midzonal vacuolization due to fatty infiltration. Changes in the thyroid consisted of reduction in follicular size, increased epithelial height from flattened cuboidal cells to columnar shape, and reduced colloid density. Changes in the high-dose group varied from mild to moderate. Changes in the kidneys were characterized by eosinophilic inclusion, enlargement and anisokariosis of the epithelial lining cells, and hyperplasia of renal tubular epithelial cells. Only the changes associated with the high-dose diet were considered to be biologically significant by the investigators. Since no dose-responses can be constructed with the histological data, this study is inadequate for use as the basis for MRL derivation.

and increases in relative kidney weights in males did not coincide with biologically significant histological changes

Chronic-Duration MRL. No chronic-duration oral data in humans or animals were located for 1,3,5-trichlorobenzene; therefore, a chronic-duration oral MRL was not derived for this compound.

of 1,2,4-trichlorobenzene and 1,3,5-trichlorobenzene

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Tables 3-1 and 3-2 and plotted in Figures 3-1 and 3-2.

Respiratory Effects. Continuous exposure of male cynomolgous monkeys to up to 100 ppm 1,2,4-trichlorobenzene vapors for 26 weeks had no significant effect on results of pulmonary function tests (static compliance, diffusion capacity, distribution of ventilation, and lung volumes) conducted in anesthetized monkeys at termination (Coate et al. 1977). Measurements of mechanical properties of the lungs conducted in unanesthetized monkeys also were not significantly affected by exposure to 1,2,4-trichlorobenzene. Histological examination of the lungs showed no treatment-related effects.

Continuous exposure of male rats to up to 100 ppm 1,2,4-trichlorobenzene vapors for up to 26 weeks did not induce significant histological alterations in the lungs (Coate et al. 1977). Similar results were reported in rats exposed to up to 200 ppm 1,2,4-trichlorobenzene vapors 6 hours/day for 15 exposures (Gage 1970) or in male rats exposed 7 hours/day, 5 days/week to up to 100 ppm 1,2,4-trichlorobenzene vapors for a total of 30 exposures (Kociba et al. 1981). Two intermediate-duration studies in rabbits exposed to up to 100 ppm 1,2,4-trichlorobenzene vapors continuously (Coate et al. 1977) or intermittently (Kociba et al. 1981) also reported no significant alterations in the lungs upon microscopic examination. Similar results were reported in dogs following intermittent intermediate-duration exposure to up to 100 ppm 1,2,4-trichlorobenzene (Kociba et al. 1981). The nasal mucosa was also examined in rats and rabbits in the Kociba et al. (1981) study.

The only information regarding 1,3,5-trichlorobenzene is from a study in male and female CD rats in which the animals were exposed 6 hours/day, 5 days/week for 13 weeks (Sasmore et al. 1983). Exposure to up to 130 ppm 1,3,5-trichlorobenzene vapors did not induce significant histological alterations in the lungs, trachea, or nasal passages.

Cardiovascular Effects. Continuous exposure of male monkeys, rats, or rabbits up to 100 ppm 1,2,4-trichlorobenzene vapors for 26 weeks did not induce significant gross or microscopic alterations in the heart (Coate et al. 1977). Exposure of male rats, dogs, and rabbits to up to 100 ppm 1,2,4-trichlorobenzene vapors 7 hours/day, 5 days/week for a total of 30 exposures during a 40-day period did not induce significant gross or microscopic alterations in the heart or aorta (Kociba et al. 1981).

Exposure of rats to up to 130 ppm 1,3,5-trichlorobenzene vapors 6 hours/day, 5 days/week for 13 weeks did not induce histological changes in the heart (Sasmore et al. 1983).

(1970) reported that rats exposed to 70 ppm 1,2,4-trichlorobenzene 6 hours/day for 15 exposures showed retarded weight gain, but no data were presented.

Exposure of rats to 1,209 ppm 1,3,5-trichlorobenzene vapors for 60 minutes resulted in 44 and 60% less body weight gain in males and females, respectively, 14 days after exposure (Jorgenson et al. 1976). Body weight was not affected in rats exposed intermittently to up to 130 ppm 1,3,5-trichlorobenzene vapors for 13 weeks (Sasmore et al. 1983).

Metabolic Effects. Intermittent exposure of rats to up to 130 ppm 1,3,5-trichlorobenzene vapors for 13 weeks did not significantly affect serum electrolyte levels or electrolyte balance (Sasmore et al. 1983).

No relevant data were located regarding 1,2,4-trichlorobenzene.

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after inhalation exposure to trichlorobenzenes.

Continuous exposure of monkeys, rats, and rabbits to up to 100 ppm 1,2,4-trichlorobenzene vapors for 26 weeks did not induce significant gross or microscopic changes in the spleen of the animals (Coate et al. 1977). Fifteen intermittent exposures (6 hours/day) of rats to up to 200 ppm 1,2,4-trichlorobenzene vapors also did not result in significant histological alterations in the spleen (Gage 1970). Similar experiments in rats, rabbits, and dogs exposed 7 hours/day, 5 days/week to up to 100 ppm 1,2,4-trichlorobenzene vapors for a total of 30 exposures during a 44-day period did not result in significant gross or microscopic alterations in the spleen, thymus, or lymph nodes (Kociba et al. 1981).

No histological alterations were observed in lymphoreticular tissues from rats exposed to up to 130 ppm 1,3,5-trichlorobenzene vapors 6 hours/day, 5 days/week for 13 weeks (Sasmore et al. 1983).

No relevant data were located regarding 1,2,3-trichlorobenzene.

NOAELs for lymphoreticular effects are presented in Table 3-1 and are plotted in Figure 3-1.

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to trichlorobenzenes.

Lethargy was reported in rats during 6-hour exposures to 70 ppm 1,2,4-trichlorobenzene vapors (Gage 1970). No such effect was observed during exposures to 20 ppm.

Continuous exposure of monkeys, rats, or rabbits to up to 100 ppm 1,2,4-trichlorobenzene vapors for 26 weeks did not induce significant gross or microscopic changes in the brain and spinal cord (Coate et al. 1977). Operant behavior tests conducted in the monkeys throughout the study showed no exposure-related alterations. Similar lack of gross or histological alterations were reported in the brain, spinal cord, and peripheral nerves from rats, dogs, and rabbits exposed intermittently to up to 100 ppm 1,2,4-trichlorobenzene vapors during a 44-day period (Kociba et al. 1981).

No histological alterations were observed in the brain and spinal cord from rats exposed to up to 130 ppm 1,3,5-trichlorobenzene vapors 6 hours/day, 5 days/week for 13 weeks (Sasmore et al. 1983).

No relevant data were located regarding 1,2,3-trichlorobenzene.

NOAELs and LOAELs for neurological effects are presented in Table 3-1 and are plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to trichlorobenzenes.

No significant gross or histological alterations were reported in the reproductive organs from male rats, dogs, and rabbits exposed intermittently to up to 100 ppm 1,2,4-trichlorobenzene vapors for 44 days (Kociba et al. 1981). It should be noted, however, that absolute and relative testes weights were significantly increased (30 and 43%, respectively) in rabbits exposed to 100 ppm (but not 30 ppm). The investigators considered this change unrelated to the test material since, as indicated above, microscopic examination did not reveal any significant histological changes.

8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

The international and national regulations, advisories, and guidelines regarding trichlorobenzenes in air, water, and other media are summarized in Table 8-1.

ATSDR has derived an intermediate-duration oral MRL of 0.1 mg/kg/day for 1,2,4-trichlorobenzene based on an increased incidence of centrilobular hepatocyte hypertrophy in male rats administered 1,2,4-trichlorobenzene in the diet for 13 weeks (CMA 1989). The MRL was derived using BMD modeling of incidence data for hepatocyte hypertrophy in male rats. The predicted dose associated with a 10% extra risk (BMD_{10}) for hepatocyte hypertrophy was 33.09 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 14.35 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

Done here

ATSDR has derived a chronic-duration oral MRL of 0.1 mg/kg/day for 1,2,4-trichlorobenzene based on an increased incidence of hepatocellular hypertrophy in male rats administered 1,2,4-trichlorobenzene in the diet for 104 weeks (Moore 1994a). The MRL was derived using BMD modeling of incidence data for ~~diffuse fatty change in female rats.~~ The predicted dose associated with a 10% extra risk (BMD_{10}) for diffuse fatty change was 23.25 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 13.33 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

Done here

What?

hepatocellular hypertrophy in male rats

EPA (IRIS 2010) has established an oral reference dose (RfD) for 1,2,4-trichlorobenzene of 0.01 mg/kg/day based on a NOAEL of 14.8 mg/kg/day for increased adrenal weights in rats exposed to 1,2,4-trichlorobenzene in drinking water (Robinson et al. 1981). The uncertainty factor used in this assessment was 1,000 (10 for extrapolation from laboratory studies, 10 for the protection of sensitive human subpopulations, and 10 to account for a lack of chronic studies). EPA's assessment was conducted in 1991.

EPA has not derived an inhalation reference concentration (RfC) for trichlorobenzenes.