SUMMARY REPORT

OF REVIEWER COMMENTS

ON THE

TOXICOLOGICAL PROFILE FOR

1,1,1-TRICHLOROETHANE

Submitted to:

The Agency for Toxic Substances and Disease Registry
Division of Toxicology
Atlanta, Georgia

Submitted by:

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SECTION 1

PEER REVIEWERS' SUMMARY REPORTS ON PROFILE

PEER REVIEWER COMMENTS FROM

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Peer Review of Toxicological Profile for "1, 1, 1-Trichloroethane"

General comments

Several corrections (including calculations) and changes are suggested in the body of the profile, figures, tables and supplemental document and should be considered during the revision of the profile.

The profile of 1,1,1-trichloethane is consistent and very comprehensive and elaborative. This is a well written document with great scientific and technical significance. The information provided in this profile is easy to understand and should be very meaningful for the intended purpose. The layout of the profile is also appropriate and easy to follow. There are some organizational and editorial lacunae, which need to be considered during its revision. The word "Chapter" used in the text for the reference is, however, not mentioned in the "Content" page(s). Although commonly used, the registered trade name "Chloroethene NU" is generally misleading, since "ethene" term is used for the unsaturated ethylenes. Therefore, a recommendation should be made to amend this anomaly.

Tables and figures 4-8 are missing or not sent with the package.

References need to be thoroughly checked for spelling, year, volume and sequence (some references are out of place). References need to be checked and format should be strictly followed (e.g., a minimum of 3 authors should be listed before using et al. in the references). The issue number given for some references should be deleted. The references in general need to be revised with proper format adopted for the profile.

Policies for usage of abbreviations and proper formats have not been practiced uniformly, particularly in the "Supplemental Documents." Several commonly used names and abbreviations of 1,1,1-TCE are used. Numerical numbers are presented in different formats (e.g. 10000 and/or 10,000). Two ways are used to summarize the results either as "Comments" or "Description and Results/comments" in the "Supplemental document." The amount of material provided in above mentioned sections also varies drastically. It appears several experts wrote "Comments" or "Description and Results/comments" in the documents separately. Therefore, a thorough and extensive editing for the both sections is required for the consistency.

Detailed comments

Reported studies relevant to child health and developmental effects are meager or none. However, various physiological and biochemical factors likely to be involved in the toxicity of 1,1,1-trichloethane and general issues relevant to child health have been considered in the "profile."

Chapter 1. Public health statement:

The public health statement is nicely worded in a best possible non technical style to be understood by lay public. On the other hand "profile" presented various facts, exposure limits and daily intake in a factual tone rather than judgmental. The major headings are stated as questions. Answers to the questions are adequately addressed, which are consistent with reminder of the text and summary statement. All the scientific terms used in the "profile" are appropriate and easy to understand.

Chapter 2. Relevance to public health:

The "profile" has clearly defined the information available in animals and humans. Text addresses all the major effects known in humans, effects reported in the animals but not in humans, and the exposure conditions likely to be of concern to humans especially around hazardous waste sites. I agree with the reports on humans and "profile" adequately addressed most of the relevant literature reports on human health effects. Calculated values of MRLs for 1,1,1-trichloroethane via inhalation and oral exposure (acute and intermediate) routes are justified and appropriate. The MRLs for chronic exposure are not calculated by the authors due to unavailability of the reliable data. No additional references are needed. I have done a literature search, myself, and found that "profile" is up-to-date. The effects only reported in the animals likely to be of concern to humans, because several of such information is not available in humans. The exposure conditions described for the human studies are explained in a detailed manner and presented a best possible scenario. Based on the available reports, no further information should be necessary at this time.

Chapter 3. Health effects:

Toxicity - quality of human studies are clearly defined and described in the beginning of each section and major limitations are also addressed in detail. Authors have done great job in compiling the health effects of 1,1,1-trichloroethane in humans and experimental animals. The conclusions drawn by the authors are justified and reflected in the "profile." Authors made it clear in the "profile" wherever derivations of MRLs was not possible due to insufficient data and/or lack of methodology. Derivation of LOAELs and NOAELs is also appropriate and authors have addressed all the deficiencies and limitations in this "profile" and followed the guidelines and regulations set by ATSDR. Statistical tests and p values are important (provides the reliability of the data) for the toxicologists, but not for the health professionals and public. Therefore, the emphasis in this issue is not very important from public point of view. In my opinion, authors have considered all the important methods/studies regarding toxicity evaluation and are in the right places in the text.

Toxicity - quality of animal studies section is the major part of the "profile" and authors have adequately addressed the design of the animal studies and provided justification regarding various animal protocols (identifying all the details such as animal numbers, species, exposure types, duration of exposure and toxicological end points/effects).

Wherever necessary, authors have provided their own judgment and reasoning to negate the utility of the study. Toxicity discussion is in detail and very clear. Authors often mention statistical significance of the data. However, the types of statistical tests used are not described, which I also don't feel necessary for the "profile." My suggestion is that relevance of toxicity of 1,1,1-trichloroethane metabolites (1,1,1-trichloroethanol and 1,1,1-trichloroacetic acid) should be discussed in explaining the toxicity manifested by the parent compound wherever appropriate in the text. For example pulmonary toxicity of the 1,1,1-trichloroethane. The authors have drawn appropriate conclusions, calculated NOAELs and LOAELs and identified toxicological effects for the studies. Comment regarding appropriateness of the statistical analysis has already been stated.

Levels of significant exposure (LSE) tables and figure are self explanatory and can be understood easily. The units and doses are also accurately presented for the route of exposure. Tables and MRI values are justifiable and so is the categorization "less serious" and "serious" for the effects cited in the LSE tables. The evaluation of the text is also done appropriately and discussed in the text. Most of the end points are critically evaluated and finally concluded well in "bottom-line" statements. Conclusions, dose-response relationship and extrapolation of animal data are well done and appropriate.

Genotoxicity data is reported largely negative and there are no conclusions drawn.

Toxicokinetics (absorption, distribution, metabolism, and excretion) of 1,1,1-trichloroethane is sufficiently described. Major organs and tissues of storage for 1,1,1-trichloroethane and its metabolites are identified. Applicable metabolic parameters supporting the data, and discussion about the differences in toxicokinetics between human and animals are adequate. Although the description is not as it has to be for the PBPK models, the information available is sufficient to be understood by a lay man and health professionals. The tables related to PBPK models were not found in the package. Therefore, a detailed critique could not be assembled. So far description is concerned; there is enough information to make sense.

Mechanisms of action mostly tell about the metabolism of the 1,1,1-trichloroethane, distribution and elimination. Various biological effects that cause toxicity are mentioned and discussed in relation to mechanism of toxic action of 1,1,1-trichloroethane. Authors have made it clear in the text. A reference to retained tricholoroethanol and/or trichloroacetic acid as their lipid conjugates should be made, although not necessary.

Text regarding "Toxicities mediated through the neuroendocrine axis" and "Children's susceptibility" is relevant and detailed based upon available information.

Biomarkers of exposure and effects are discussed in detail and pointed out several bottlenecks in their development. Authors have drawn the far reaching conclusions, which are perfectly correct to my knowledge. But metabolic products of 1,1,1-trichloroethane, trichloroethanol and trichloroacetic acid should be mentioned in some extent. Both metabolites may be biotransformed via nonoxidative metabolism to form conjugate with endogenous substrates (fatty acids, phospholipids and cholesterol)

containing carboxylic, amino and hydroxyl group(s). The product of these reactions could be highly lipophilic and likely to be retained in the target organs. Their levels in the target organs may be reflected in the plasma as has been shown in the alcoholic subjects (Ansari et al., 1995; Kaphalia and Ansari, 2001). These esters may also have toxic potential once reached to a critical concentration in the target organ(s). Therefore lipid conjugates of metabolites of 1,1,1-trichloroethane could be one of the explanation of mechanism of their retention in the fatty tissues. Authors can look critically at "lipid conjugation of xenobiotics" as a mechanism of target organ toxicity as well as bioaccumulation upon long term exposure. Such conjugation reactions can also cause changes in the membrane permeability, cellular ATP depot and neurotransmission as described on page 82 of the profile. Authors can provide some speculative ideas about this alternate mechanism of toxic action of 1,1,1-trichloroethane.

Interaction with other chemicals is well justified. For example ethanol potentates lethality and behavioral effects of 1,1,1-trichloroethane. Such potentiation is also explained well via a biochemical mechanism involving cyp 2E1. Adequate discussions of interactions and their mechanism are provided in the profile.

Unusually susceptible population is discussed appropriately and also included a reference to children's susceptibility to 1,1,1-trichloroethane toxicity. Authors have accumulated most relevant information regarding children's susceptibility to 1,1,1-trichloroethane toxicity in terms of biochemical and physiological status.

Methods for reducing toxic effects and the peak levels of 1,1,1-trichloroethane, and enhancing its elimination from the body are focused. Both sections are well described and provided with conceptual approaches. Rationale provided for reducing the toxic effects of 1,1,1-trichloroethane are also in detail and easy to understand. However, no information is provided regarding any hazard associated with the treatment of infants and children. Body burden could be significantly higher from trichloroethanol and trichloroacetic acid or their conjugated metabolites rather than parent compound under chronic exposure conditions. This possibility is not discussed in the profile. Authors have discussed pros and cons of the most of the treatment plans and their side effects. How the stored xenobiotics in the target organs eliminated or mobilized without any adverse effects is not discussed.

Adequacy of the data base for 1,1,1-trichloroethane is well addressed. Except genotoxicity, each of the end points has been investigated in animals by inhalation and oral routes. Fewer end points have been studied following dermal exposure. The data base deficiencies, literature cited as well as needs are pointed out.

Chapter 4. Chemical and physical properties:

Although, tables 4-1 and 4-2 for summarized chemical identity and physical and chemical properties is a good mean of presentation. However, both tables were not found in the package. Structure of 1,1,1-trichloroethane and its metabolic products, and suitable

schematic presentation should help reader understand better the toxicokinetics and target organ toxicity.

Chapter 5. Production, import/export, use, and disposal:

Production, import/export, use, and disposal of 1,1,1-trichloroethane appear to be sound, though brief. The table 5-1 was not found in the package. Although not available, import/export data of 1,1,1-trichloroethane should have been important, since the last reported data was in 1993.

Chapter 6. Potential for human exposure:

Authors have presented various ways in which released substances are modified by time and environmental processes, which may pose potential for human exposure via different pathways. The information provided is more than sufficient and well organized. The text appropriately traced the point of release until it reached to receptor population
The information regarding transport, partitioning, transformation, biotransformation and degradation of the substance in each medium/matrix is pertinent. Is their any information regarding food chain bioaccumulation of 1,1,1-trichloroethane and/or its metabolites? Other information such as proper units, sources and exposure routes for the general population and occupations is also sufficient and reliable.

Chapter 7. Analytical methods

Although table 7-1 was not found in the package, over all text describing the quantitation of 1,1,1-trichloroethane is to the point and just. The concept of analytical techniques for the analysis of 1,1,1-trichloroethane remains same. Analysis of metabolites trichloroethanol and trichloroacetic acid as well as their conjugates, particularly lipid conjugates, is not discussed. There could be some HPLC methods for both metabolites from biological matrix; however, author did not pay much attention in this direction, because 1,1,1-trichloroethane is itself a major marker of exposure. Descriptions regarding sampling issues for the substance are nicely presented. Other concerns regarding identification of data needs are justified.

Chapter 8. Regulation and advisories

Although the table 8-1 was not found with the package, international, national and state regulations and guidelines are referenced well and I am not aware of any other European and other international agencies.

Chapter 8. References

A number of changes, typos and format related questions are already marked or suggested in the text. All the references are up to date and appropriate. No additional references are needed at this time.

Other material included with this profile

IRIS file: No comments

Revised tables and figures: Only tables 3-1 to 3-3 and figures 3-1 to 3-2 are enclosed with the package. The suggested changes and corrections are marked in the tables and figures.

Supplemental document has lots of variations so far description is concerned. Authors write "comments" or "description and results." The amount of information is also quite variable (too small and too large). The later should be coupled in order to avoid repetition and large text. Generally, description or comments should not be more than 2-5 lines depending upon the information available. Therefore, a massive editing is needed for the text provided in the supplemental document under the heading "Comments or Results and Discussion/comments." 1,1,1-trichloroethane is abbreviated as 1,1,1-TCE or just TCE. This should be straitened out in comments or description segments of the supplemental document. The calculations used for the dose should be checked thoroughly. I have marked suggestions and correction in the text wherever necessary. Authors should take a note of the all the marked text or changes while revising the profile. The reference # provided in the supplemental documents denotes what? It is not clear from the reference list or whatever.

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Dr. KRISHNAN'S REVIEW OF ATSDR'S TOXICOLOGICAL PROFILE ON 1,1,1-TRICHLOROETHANE

General Comments:

This document provides a very good synthesis and interpretation of available information on the uses, production, environmental fate and distribution, exposure pathways and sources, health effects as well as available norms for 1,1,1-trichloroethane from a public health perspective. MRL derivations, though limited, have been appropriately done but require better justification of the use of specific uncertainty factors (see below for suggestions). The authors should be commended for doing an excellent job of treating confusing and conflicting data to draw appropriate weight of evidence statements useful for the audience, and for preparing high quality summary statements that reflect the bottom-line of multiple studies and observations relating to each health endpoint

The following are my responses to the specific questions.

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

No. In fact some statements relating to children are inaccurate and should be corrected as suggested (see specific comments).

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

No.

CHAPTER 1. PUBLIC HEALTH STATEMENT

- The tone of the chapter should be factual rather than judgmental. Does the chapter present the important information in a non-technical style suitable for the average citizen?

  Yes.

- Major headings are stated as a question. In your opinion, do the answers to the questions adequately address the concerns of the lay public? Are these summary statements consistent, and are they supported by the technical discussion in the remainder of the text?

Yes. The bottomline statements are appropriately made. However, a judgmental statement such as air being the most important medium of exposure might be appropriate.

- Are scientific terms used that are too technical or that require additional explanation?

No.

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

Section 2.1 Background environmental exposures

Appropriate statements have been made regarding the uses, background levels, environmental exposure and biomonitoring of 1,1,1-trichloroethane.

Section 2.2 Summary of health effects

Toxicity – Quality of Human Studies

- Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? If not, were the major limitations of the studies sufficiently described in the text without providing detailed discussions. If study limitations were not adequately addressed, please suggest appropriate changes.

yes

- 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? If not, did the text provide adequate justification for excluding NOAELS/LOAELs including, but not limited to, citing study limitations?

Yes

- Were the appropriate statistical tests used in the studies? Would other statistical tests have been more appropriate? Were statistical test results of study data evaluated properly? NOTE: As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data.

The statistical significance mentioned in the studies is referred to in lay terms in the document in an appropriate manner.

- Are you aware of other studies which may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.

No

Toxicity – Quality of Animal Studies

- Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)?

Yes; the presented detail is sufficient for the purpose of the document.

- Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

yes

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

Appears so.

- Were all appropriate NOAELs and LOAELs identified for each study? Were all appropriate toxicological effects identified for the studies? If not, please explain.

Identified appropriately where relevant and available.

- If appropriate, is there a discussion of the toxicities of the various forms of the substance? If not, please give examples of toxicological effects that might be important for forms of the substance.

N/A

- 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? NOTE: As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data.

The statistical significance mentioned in the studies is referred to in lay terms in the document in an appropriate manner.

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.

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? Please offer suggestions to improve the effectiveness of the LSE tables and figures and the "User's Guide".

Yes. In all the tables (3.1, 3.2, and 3.3), "chemical form" in the last column should be deleted. Similarly, "(specific route)" in the third column of these tables may be deleted, since the title of the table specifies the route (inhalation, oral, dermal).

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

Yes. The numbers plotted in the figures are all found in the appropriate entries in the accompanying tables.

° 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?

Page A-7

The calculated intermediate oral MRL of 17.7 mg/kg/d has been rounded off to 20 mg/kg/d. It does not appear appropriate to round the MRLs to the nearest tens.

Page A-3

The acute inhalation MRL section should include a justification of the non-adjustment for exposure duration. Since Cmax (or steady-state concentration) is likely to be related to acute effects, there is no reason to believe that it will change with increasing exposure concentrations. Therefore the non-use of an exposure duration factor is appropriate.

Page A-6

In establishing the intermediate inhalation MRL, HEC is appropriately derived. However, the use of a full factor of 10 (for animal-human extrapolation) is not defensible given that the pharmacokinetic component has already been accounted for already during the HEC calculation. This aspect should be appropriately addressed. The authors may want to look into some examples of EPA's RfC derivations.

Why were the rat NTP studies (26r, 31r, 32r in figures 3-2) not considered in the derivation of an intermediate duration MRL for the oral route?

Evaluation of Text

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

Appropriately so

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

yes

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

Done very well

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

yes

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

Not very much, as limited by data

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

To some extent as permitted by available data

Section 3.4 TOXICOKINETICS

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

Yes

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

Yes

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

Yes. However, not all efforts on PK modeling have been reviewed or presented. But the key aspects of the PK behavior have been adequately captured.

- Is there adequate discussion of the differences in toxicokinetics between humans and animals? What other observations should be made?

Differences in rate of metabolism and blood:air partition coefficient have been appropriately high lighted. Interspecies differences in physiological determinants of trichloroethane PK (e.g., alveolar ventilation rate) may also be highlighted.

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

yes

- If applicable, is there a discussion of the toxicokinetics of different forms of the substance (e.g., inorganic vs organic mercury)?

N/A

Section 2.4 MECHANISMS OF ACTION

There is an adequate discussion of the mechanism of action. It is only of limited use, however.

Section 2.5 RELEVANCE TO PUBLIC HEALTH

- Do you agree with those effects known to occur in humans as reported in the text?

Yes

- Are the effects only observed in animals likely to be of concern to humans?

NA

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

Yes

Section 2.6 and 2.7 ENDOCRINE DISRUPTION AND CHILDREN'S SUSCEPTIBILITY

Relevant but succinct discussions are found in the document. Some statements relating to children should be corrected as suggested (see specific comments at the end of this document).

Section 2.8 BIOMARKERS OF EXPOSURE AND EFFECT

° Are the biomarkers of exposure specific for the substance or are they for a class of substances? If they are not specific, how would you change the text?

Appropriately presented

° Are there valid tests to measure the biomarker of exposure? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.

Discussions relating to trichlorethane in exhaled air, trichloroethane in urine and urinary metabolites are appropriate.

° Are the biomarkers of effect specific for the substance or are they for a class of substances?

na

° Are there valid tests to measure the biomarker of effect? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.

no inconsistencies in the text regarding biomarkers of effect/exposure.

Section 2.9 INTERACTIONS WITH OTHER SUBSTANCES

° Is there adequate discussion of the interactive effects with other substances? Doe the discussion concentrate on those effects that might occur at hazardous waste sites? If not, please clarify and add additional references.

Yes

° If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? If not, please clarify and provide any appropriate references.

Yes, as limited by data availability. There is an excellent study by Tardif and Charest-Tardif on an interaction involving trichloroethane. It was published a couple of years ago in Toxicological Sciences.

Section 2.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

- Is there a discussion of populations at higher risk because of biological differences which make them more susceptible? Do you agree with the choices of populations? Why or why not? Are you aware of additional studies in this area?

The discussion is appropriate.

Section 2.11 METHODS FOR REDUCING TOXIC EFFECTS

- Is the management and treatment specific for the substance, or is it general for a class of substances?

Appropriate.

- Is here any controversy associated with the treatment? Is it a "well-accepted" treatment?

N/A

Section 2.12 ADEQUACY OF THE DATABASE

Existing Information on Health Effects

- Do you know of other studies that may fill a data gap? If so, please provide the reference.

No

Identification of Data Needs

- Are the data needs presented in a neutral, non-judgmental fashion?

Yes

- Do you agree with the identified data needs?

Yes

- Does the text indicate whether any information on the date need exists?

Yes

° Does the text adequately justify why further development of the data need would be desirable or conversely, justify the "inappropriateness" of developing the data need at present?

NA

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

- Are you aware of any information or values that are wrong or missing in the chemical and physical properties tables?

This table was missing in the package. It should be included in the final document, and is not considered to be a critical element to this peer review.

Is information provided on the various forms of the substances? If not, please explain.

N/A

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

- Are you aware of any information that is wrong or missing? If so, please provide copies of the references and indicate where (in the text) the references should be included.

No. Available information is adequately presented.

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

- Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites?

Yes

- Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media?

Yes

- Does the text provide information on levels monitored or estimated in the environment, including background levels?

  Yes

- Does the text describe 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?

  Yes

Identification of Data Needs

° Are the data needs presented in a neutral, non-judgmental fashion?

  Yes

° Do you agree with the identified data needs?

  Yes

° Does the text indicate whether any information on the data need exists?

  Yes, clearly so

° Does the text adequately justify why further development of the data need would be desirable or conversely, justify the "inappropriateness" of developing the data need at present?

  Yes

CHAPTER 6. ANALYTICAL METHODS

- Are you aware of additional methods that can be added to the tables? If so, please provide copies of appropriate references.

  No

- Have methods been included for measuring key metabolites mentioned previously in the text?

Not really. A couple of summary statements regarding the analytical methods for metabolites should be included.

- If unique issues related to sampling for the substance exist, have they been adequately addressed in the text? What other discussion should be provided?

  N/A

CHAPTER 7. REGULATIONS AND ADVISORIES

- Are you aware of other regulations or guidelines that may be appropriate for the table?

  No.

CHAPTER 8. REFERENCES

References in the text are presented in the alphabetical order rather than the chronological order. Is this an error or the way it's done in Profile documents?

The following human PK study should be considered and included in the document:

Laparé, S., Tardif, R., and Brodeur, J. (1995). Effect of various exposure scenarios on the biological monitoring of organic solvents in alveolar air. II. 1,1,1-trichloroethane and trichloroethylene. International Archives of Occupational and Environmental Health **67**, 375-394.

SPECIFIC COMMENTS

The following minor corrections relating to typo or style should be corrected:

Page 34, line 4

"Statistically significantly" should be reworded.

Page 34, lines 10-11

Verbs are of two different tenses (is & was).

Page 34, line 25

The exposure concentration may be added for clarification.

Page 35, line 11

on or in a variety of species.....

Page 35, line 16

may be re-written as: male rats, male mice or female mice...

Page 35, line 26

This sentence must include reference to "body weight gain"

Page 36, lines 9 & 10

Combine the two sentences here, by putting **and**

Page 45, lines 5-6

The names of authors need not be repeated in case of multiple citations (e.g., Rohr Indus Inc., 1987a, 1987b).

Page 45, line 8

May be rewritten as: Statistically significant increases in....

Page 54, line 31

Statistical significance is for which treatment groups?

Page 47, line 1

does this refer to lowest LD50 or really a LOAEL?

Page 47, line 24

"drank a single 600 mg/kg dose of..." is awkward and re-wording is suggested.

Page 52, line 27

The doses should be specified

Page 53, line 20

"3 mg/kg/day in drinking water" is awkward and should be re-worded

Page 53, line 22

.....was noted **in** male rats....

Page 55, line 20

"2.5 mg/kg/day in drinking water" is awkward and should be re-worded

Page 57, line 6

The number of animals may be replaced with % response.

Page 58, line 12

..reliable **dermal** study.....

Page 59, para 1

Appropriate reference(s) may be added

Page 65, line 14

Appropriate reference(s) may be added

Page 66, lines 4-6

Re-write/re-read this sentence.

Page 67, lines 23-25

.."Nolan et al. (1984).....95% of steadystate" should be deleted. It is neither essential (given the preceding and subsequent statements) nor is technically accurate.

Page 72, line 8

Respective doses ..... ? should be specified

Page 73, line 7; rewording suggested

.....can be reductively dechlorinated, to a limited extent, to radical intermediates...

Page 73, line 12; rewording suggested

.....because it apparently represents a very minor metabolic pathway.

Page 74, line 17

0.0 ? check.

Page 78, line 15

.....and observed values of the amount of.....

Page 79, line 14

Low rate

Page 79, line 26

The sentence should be reworded such that it does not give the impression that CO2 is a major/primary metabolite.

Page 80, line 19

.....than 1,1,1-trichloroethane.....

Page 81, lines 1-2; page 72, para 3

The differential effects of phenobarbital on trichloroethane metabolism is likely to be dependent upon exposure concentration, due to relative roles of isozymes (low affinity vs high affinity). I vaguely remember an excellent article by Tamie Nakajima.

Page 90, lines 1-6

The relevance of this paragraph is unclear.

Page 93; line 18

...absorption of 1,1,1-trichloroethane.....

Page 31, line 13

Length of exposure may be specified

Page 109, line 6

Lakes Charles should read Lake Charles

Page 115, para 3; Page 113 para 3

Past tense in this para may be changed to presence tense.

Page 129, line 3

The extent of transfer via mother's milk is very low as mentioned elsewhere (Fisher et al.)

Page 134, lines 9-10; page 129, lines 18-20

This sentence is probably not accurate, since children will also exhale due to high alveolar ventilation rate. Differential rate of metabolism, if at all, is

Page 141, para 3

Does not really reflect data needs for refining the use of urinary concentration of trichloroethane as a biomonitor.

PEER REVIEWER COMMENTS FROM

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August 13, 2004

Mr. Andy Lord
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Re: Draft Toxicological Profile Document on 1,1,1-Trichloroethane

Dear Mr. Lord:

Thank you for the opportunity to review this document. I am two days late in the review and I apologize for that. As I discussed with you by telephone earlier this week, it took me somewhat longer than the allotted time to conduct the review.

Let me say at the outset that, initially, I attempted to verify all statements in the document by retrieving the appropriate reference from the CD-ROM files and checking the accuracy of the statements. This was done for nearly all references through page 64 of "Draft 2 of Profile" as indicated by the presence of a small check in red ink by the individual references. It became apparent however, that I would not have sufficient time to do this throughout the document. Thus, as you suggested, I only accessed references on subsequent pages when I felt that the comments needed clarification. You should also be aware that I did not receive any of the numbered tables after Table 3.2.

The following are my responses to specific questions in the "Guidelines for Peer Review of ATSDR'S Toxicological Profiles".

1. **Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be?**

   Ans: I could not retrieve any data that was not covered in the profile.

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

   Ans: The discussion of issues in the profile relevant to child health is quite extensive. I cannot think of additional issues that should have been addressed.

College of Medicine and Public Health / The Ohio State University Hospital / The Arthur G. James Cancer Hospital and Richard J. Solove Research Institute / Unversity Hospitals East / OSU Harding Hospital / Primary Care Network

Page 2; Gary Stoner, Ph.D.

Chapter 1. Public Health Statement

1. **Does the chapter present the important information in a non-technical style suitable for the average citizen?**

   Ans: Yes, it is well written and in terminology that should be understood by the average citizen.

2. **In your opinion, do the answers to the questions adequately address the concerns of the lay public? Are these summary statements consistent, and are they supported by the technical discussion in the remainder of the text?**

   Ans: The answer to both of these questions is an unqualified "yes".

3. **Are scientific terms used that are too technical or that require additional explantation?**

   Ans: No

Chapter 2. Relevance to Public Health

1. **Do you agree with those effects known to occur in humans as reported in the text?**

   Ans: Yes. The effects described have been documented in multiple case reports, and in at least one important experimental study in which humans were exposed to 1,1,1-TCE. There is substantial agreement among the different reports to substantiate that the effects described are accurate. The sequence in which these effects occur; e.g.; neurological vs. cardiological vs. respiratory is still a matter of some speculation however, the effects described are accurate.

2. **Are the effects only observed in animals likely to be of concern to humans?**

   Ans: The clinical and behavorial effects observed in animals also occur in humans; i.e., the neurological, cardiovascular and respiratory effects. There do not appear to be any major differences between animals and humans in these effects. Certain tissue-specific effects seen in animals such as 1,1,1,-TCE-induced fatty liver in rats and the accumulation of glial fibrillary acid (GFA) protein in the cerebral cortex of gerbils however, have not been documented in humans and are probably related to the high doses of compound administered over long periods of time. It's questionable whether humans would be exposed to high enough levels of 1,1,1-TCE over a long enough time to acquire these effects. The carcinogenicity data in animals, so far, have been negative, and epidemiological

data in humans, although inadequate, have not revealed a carcinogenic effect of 1,1,1-TCE in humans. Thus, with respect to carcinogenicity, the available data in animals and humans would suggest that 1,1,1-TCE is not likely to be carcinogenic in humans. More research is required to confirm this.

3. Have exposure conditions been adequately described?

Ans: The exposure conditions (route, duration, level) in animals have been well described. Exposure conditions in humans have also been well described, especially around hazardous waste sites. The routes and levels of exposure vary quite dramatically as a function of proximity to hazardous waste sites. The levels of exposure in humans are measured by examination of metabolites of 1,1,1-TCE in urine and are likely to be reasonable approximations.

Chapter 3. Health Effects

1. **Toxicity – Quality of human studies.**
   a) **Were adequately designed human studies identified in the text?** Most of the reports in humans have been from case reports of individuals who either died from acute exposure to the agent (usually inhaling the compound purposely) or who exhibited fairly extensive toxic effects (but not lethal effects) from accidental exposure. In a few experimental studies, humans were exposed to 1,1,1-TCE at lower concentrations for different periods of time, generally by inhalation. Exposure data from most of the case reports are estimations. From the experimental studies however, the exposure data are accurate and the exposure occurred over a sufficient period to observe some of the effects seen in acute exposure (although not as dramatic). The limitations of the human studies is that they have not involved all routes of exposure (e.g., the dermal route). In addition, the epidemiological studies have not been designed adequately to assess the potential carcinogenic effects in humans.

   b) **Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the profile?**
   The conclusions of the authors of the studies are appropriate and they are accurately reflected in the profile. The profile does an excellent job of summarizing the conclusions of the authors.

   c) **Were all appropriate NOAELs and/or LOAELs identified for each study?**
   Yes

d) **Were the appropriate statistical tests used in the studies?**
I am not a statistician however, it appeared that the appropriate statistical tests were used in the experimental studies in humans and animals. The case reports had too few individuals to make statistical inferences.

e) **Are you aware of other studies which may be important in evaluating the toxicity of the substance?**
No

2. **Toxicity- Quality of animal studies.**

a) **Were adequately designed animal studies identified in the test?**
Yes, in general, the animal studies were well designed.

b) **Were the animal species appropriate for the most significant toxicological endpoint of the study?**
Yes. The animal species used for most studies were mice and rats and they were appropriate for the toxicological endpoints. However, it would be appropriate to conduct exposure studies in primates using dose levels of the compound seen in high exposure sites, and multiple routes of administration (inhalation, dermal and oral). Such studies in primates would be "less risky" than studies in humans and could be done over longer periods to assess the effects of more chronic exposures to the agent.

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

Yes, the conclusions of the authors of the animal studies appeared to be correct based upon the data presented, and they are accurately reflected in the text.

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

Yes to both questions.

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

1,1,1-TCE is metabolized very slowly in the body to two metabolites; trichloroethanol and trichloroacetic acid. These compounds are excreted in the urine. Although the potential toxic effects of these compounds were not discussed, the available data suggest that it's the toxic effects of 1,1,1-TCE itself and not its metabolites that are important.

e) **Were the appropriate statistical tests used in the interpretation of the animal studies?**

Yes, and the data were evaluated properly.

f) **Are you aware of other studies that may be important in evaluating the toxicity of the substance?**

No

3. **Levels of Significant Exposure (LSE) Tables and Figures.**

Are the LSE tables and figures complete and self-explanatory? Yes and the users guide explains clearly how to use them. The exposure levels are accurately represented for the route of exposure.

Do you agree with the categorization of "less serious" and "serious" for the effects cited in the LSE tables? Yes, I think this is a very useful and practical way of categorizing the effects.

If MRLs have been derived, are the values justifiable? Yes, I think the MRLs that have been derived are well justified based upon the data.

If no MRLs have been derived, do you agree with the data to support such a derivation? Yes

4. **Evaluation of Text:**

a) **Have the major limitations of the studies been adequately and accurately addressed?** Yes

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

c) **Have "bottom-line" statements been made regarding the relevance of the endpoint for human health?** Yes, very adequately.

Are the conclusions appropriate for the overall database? Yes

d) **Has adequate attention been paid to dose-response relationships for both human and animal data?** Where data have been available from human studies, attention has been paid to dose-response relationships. For animal studies, the answer is Yes.

e) **Has animal data been used to draw support for any known human effects? If so, critique the validity of the support.** Animal data has been used extensively to draw support for any known human effects. For example, the uptake and distribution of 1,1,1-TCE in animals is very rapid just as in humans, irrespective of the route of exposure. Both animals and humans metabolize the compound very slowly, and in animals and humans, most of the compound is excreted unmetabolized through the lungs. Many of the biological effects of the compound are similar in animals and humans, particularly in rats. Acute exposure to the compound leads to a reduction in blood pressure, cardiac arrhythmia and respiratory distress in both animals and humans. Animals experience neurological effects of the compound much like humans. The compound does not appear to be a carcinogen in animals and there is no epidemiologic data to suggest that it is a carcinogen in humans. These examples of similar effects in animals and humans suggest that the extrapolation of animal data to humans has substantial validity.

4. **Section 3.4. Toxicokinetics.** The answer to all of the questions in this section is Yes. It is very well written and inclusive.

5. **Section 3.5. Mechanisms of Action.** This section provides a brief overview of the known mechanisms of the metabolism, absorption, distribution and excretion of the compound in animals, followed by a discussion of substances (e.g., ethanol) which affect these mechanisms. All possible mechanisms of action have been discussed.

6. **Section 3.8. Biomarkers of Exposure and Effect.** The biomarkers of exposure are specific for 1,1,1-TCE since they are the compound itself and its two metabolites. These biomarkers can be measured very accurately in urine using standard chemical methods. The biomarkers of effect are somewhat less specific than those of exposure since compounds other than 1,1,1-TCE can elicit similar biological effects. There are valid tests to measure the multiple biomarkers of effect.

7. **Section 3.9. Interactions with Other Chemicals.** There is an adequate discussion of the effects of other compounds such as ethanol on the metabolism and biochemical effects of 1,1,1-TCE. The text discusses the available data on

the known interactions of these chemicals with 1,1,1-TCE however, this data is not extensive.

8. **Section 3.10 Populations that are Unusually Susceptible.** The high risk populations have been identified as alcohol drinkers, diabetics, individuals with cardiovascular disease or impaired respiratory function, and young people with actively developing nervous systems. The rationale for high risk of these groups is reasonable, although not substantiated by experimental investigations. In general, I agree with the choice of these populations given the biological effects of the agent in humans. I am not aware of additional studies in this area. One might conjecture that differences in the ability to metabolize 1,1,1-TCE would be important for its biological effects, but it is poorly metabolized in animals and in humans so any differences may not be relevant.

9. **Section 3.11 Methods for Reducing Toxic Effects.** The first part of this section provides a very general discussion of treatments to reduce toxic effects of 1,1,1-TCE; e.g., administration of milk or water to dilute the gastrointestinal tract contents. These treatments are not necessarily specific for 1,1,1-TCE but for many compounds of like nature that one might be exposed to. There do not appear to be any hazards associated with the treatment of infants and children with agents that would reduce toxicity.

   There do not appear to be any treatments available to prevent 1,1,1-TCE itself from reaching the target organs. The compound is rapidly cleared from the body through the respiratory system, and its not clear that any specific treatments would accelerate this. Moreover, as stated above, very little metabolism of the compound takes place. Probably ventilation of the lungs would be the most effective method to reduce exposure to it. There is no controversy associated with any of the proposed methods of treatment. They would either result in diluting the compound to reduce exposure or facilitate its removal through the lungs. There do not appear to be any hazards associated with the treatment of children or infants to reduce toxic effects. There do not appear to be any treatments to prevent adverse effects as the substance is being eliminated from the major organs/tissues where it has been stored. Again, since it is so rapidly eliminated, the focus has been on either diluting it to reduce exposure or to promote its elimination through the lungs.

   There do not appear to be treatments available to prevent 1,1,1-TCE from reaching the target organ(s) as indicated above. There is no "well accepted" treatment and there do not appear to be any hazards associated with treatment of children and infants.

10. **Adequacy of the Database.** One of the major concerns with this section is that it proposes a large number of additional studies, both in animals and humans, to further evaluate the potential toxic and other effects of 1,1,1-TCE. In view of the fact that production of 1,1,1-TCE was supposed to have been stopped in

January, 2002, one wonders why it is essential to conduct extensive additional studies with it? Even though production has not stopped, and that a decision might be made to continue to use the compound in the medical and aviation industries, it seems like extensive additional studies may not be warranted. The compound is quite volatile and, for the most part, should be eliminated from the soil, air and water over time.

a) **Do you know of other studies that may fill a gap?** No

11. Identification of Data Needs.

a) **Are the data presented in a neutral, non-judgmental fashion?** Yes, I did not find evidence of bias.

b) **Do you agree with the identified data needs?** I do not agree with all of the identified data needs as presented in the profile. For example, the proposed acute oral toxicity studies with neurological and vascular endpoints (presumably in animals) on page 98 seem unnecessary. We already have extensive data on the effects of acute exposure of this compound in humans. The proposed acute dermal studies are also probably not necessary since it is unlikely that humans will be exposed to high doses of 1,1,1-TCE through either the dermal or oral route (unless they purposely expose themselves). The intermediate exposure studies would seem to be more reasonable since they would more closely mimic human exposure. I agree that studies that attempt to determine threshold effect levels for inhalation, oral and dermal exposure would be valuable for risk extrapolation purposes. The available carcinogenicity data do not suggest that 1,1,1-TCE is a carcinogen in animals. Although they could have been done more extensively, I don't think there is sufficient rationale to propose multiple additional long-term carcinogenicity studies in animals. It will also be difficult to establish the carcinogenicity of the compound in humans by "well designed" epidemiological studies since exposure levels vary markedly in the population and exposure to 1,1,1-TCE is confounded by exposure to multiple other agents in the environment. If 1,1,1-TCE were a substantial carcinogen in humans, the available epidemiologic data would probably have detected this. Similarly, due to multiple exposures, it's also questionable whether tests of chromosomal aberrations in peripheral lymphocytes in humans would be informative. In addition, this agent seems to be only mildly genotoxic. An inhalation study of reproductive function in animals is likely to be valuable for assessing reproductive toxicity, since that is the predominant route of human exposure to the compound. The proposed immunotoxicity studies do not appear warranted since exposure of humans to high levels of the

compound in case reports have not documented marked immunosuppressive effects of the compound. In view of the strong and irreversible effects of the compound on the nervous system, I strongly agree with the proposed in-depth studies of its effects on neurological structure and function. I'm not certain however, that epidemiological studies would provide useful information on the levels required to produce neurological effects in humans since they would require a significant number of humans exposed predominately to 1,1,1-TCE itself to produce definitive results. This might not be possible. The proposed human dosimetry studies to correlate 1,1,1-TCE levels in human tissues with chronic health effects are highly questionable given the potential toxic effects of this compound. It would be preferable to conduct these studies in primates.

12. **Chapter 4. Chemical and Physical Information.** Unfortunately, I was not provided with any Tables beyond Table 3.2. Thus, I cannot determine if any information is missing or values are incorrect.

13. **Chapter 5. Production, Import/Export, Use and Disposal.** I am not aware of any data that is missing from this chapter.

14. **Chapter 6. Potential for Human Exposure.** The answer to all of the questions in the first sentences of this section is Yes. This is a well written and informative section. I have no additions.

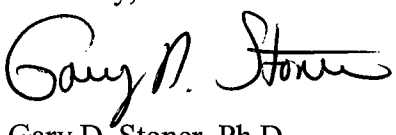
15. **Chapter 7. Analytical Methods.** These are exceptionally well described. Since I didn't receive the tables, I don't know if other methods would apply. However, the description of the available methods in the text is good, and the methods are both sensitive and reliable. The pitfalls of each method are well described. One concern is that the methods vary enough in sensitivity that, for a given study in which a control and exposed population is being compared, it would be important to use only one method for measurement. In addition, given the volatility of 1,1,1-TCE, it would be important to store samples to be evaluated in a standard manner, preferably frozen. The methods for measuring the key metabolites of 1,1,1-TCe have been mentioned.

16. **Chapter 8. Regulations and Advisories.** I did not receive the table. Thus, I don't know whether there are other regulations and guidelines that might be appropriate.

17. **Chapter 9. References.** I found no additional references that provide new data.

Thank you again for the opportunity to review this document. I understand that this information is confidential.

Sincerely,



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SECTION 2

ADDITIONAL REFERENCES AND DATA SUBMITTED BY THE PEER REVIEWERS

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SECTION 3

ANNOTATED PAGES FROM PEER REVIEWERS' PROFILE DOCUMENTS

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α-trichloromethane. Its registered trade names are chloroethene NU® and Aerothene TT®. It is a colorless liquid with a sweet, sharp odor. 1,1,1-Trichloroethane dissolves slightly in water. The liquid evaporates quickly and becomes a vapor in the air. Most people begin to smell 1,1,1-trichloroethane in the air when levels reach 120 –500 parts ~~of 1,1,1-trichloroethane~~ per one million parts ~~of~~ in the air (ppm). If the chemical makes up 8–10.5% (80,000–105,000 ppm) of the air, 1,1,1-trichloroethane can burn easily when it comes in contact with a spark or flame. If the vapor burns at high temperatures such as those produced during welding operations, it can produce a poisonous gas known as phosgene. Because of its tendency to evaporate easily, the vapor form is most commonly found in the environment. 1,1,1-Trichloroethane also can be found in soil and water, particularly at hazardous waste sites.

1,1,1-Trichloroethane was used in commercial products, mostly to dissolve other chemicals. About 800 million pounds were produced in 1990, but less is being made today. No 1,1,1-trichloroethane is supposed to be manufactured domestically after January 1, 2002 in the United States because it affects the ozone layer. 1,1,1-Trichloroethane had many industrial and household uses. It was often used as a solvent to dissolve other substances, such as glues and paints. In industry, it was widely used to remove oil or grease from manufactured metal parts. In the home, it used to be an ingredient of products such as spot cleaners, glues, and aerosol sprays.

You will find detailed information on the chemical properties of 1,1,1-trichloroethane in Chapter 4. Chapter 5 describes production data and the uses of 1,1,1-trichloroethane.

No "chapter" word is mentioned in "Content"

1.2 WHAT HAPPENS TO 1,1,1-TRICHLOROETHANE WHEN IT ENTERS THE ENVIRONMENT?

Most of the 1,1,1-trichloroethane released into the environment enters the air, where it lasts for about 6 years. Once in the air, it may travel to the upper part of the earth's atmosphere, which is called the stratosphere. There, sunlight breaks it down into other chemicals that may reduce the stratospheric ozone layer. This ozone layer blocks certain damaging ultraviolet rays of the sun

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO 1,1,1-TRICHLOROETHANE IN THE UNITED STATES

1,1,1-Trichloroethane is a synthetic chemical. In 2003, the estimated capacity of the commercial production of 1,1,1-trichloroethane in the United States was 510 million pounds (SRI 2003). Under the Clean Air Act as amended in 1990, all production of 1,1,1-trichloroethane was scheduled to cease as of January 1, 2002 (EPA 2004m). It may be used for essential applications such as medical devices and aviation safety (for the testing of metal fatigue and corrosion of existing airplane engines and other parts susceptible to corrosion) until January 1, 2005. 1,1,1-Trichloroethane was predominantly used as a chemical intermediate in the manufacture of hydrochlorofluorocarbons (HCFCs). It was also commonly used in vapor degreasing and cold cleaning, adhesives, coatings and inks, textiles, and electronics (CMR 1995).

1,1,1-Trichloroethane was released to the environment during the course of its manufacture, formulation, and use. It was frequently detected in the atmosphere and in water. In 2001, environmental releases of 1,1,1-trichloroethane reported under the EPA Toxics Release Inventory (TRI) program were about 207 thousand pounds in air emissions, 27 pounds in water discharges, 5 pounds in underground injection discharges, and 169 pounds in releases to land (TRI01 2004).

Monitoring studies of the ambient air levels of 1,1,1-trichloroethane in urban areas have reported concentrations in the range of 0.1–1 ppb, while the concentrations in rural areas have been reported to be <0.1 ppb (Table 6-3). Representative data taken from five geographic areas located throughout the United States report indoor concentrations of 0.3–4.4 ppb and outdoor concentrations of 0.11–0.92 ppb (Pellizzari et al. 1986). A more recent EPA region V (Minnesota, Wisconsin, Michigan, Illinois, Indiana, and Ohio) National Human Exposure Assessment Survey (NHEXAS) detected a mean concentration of 1,1,1-trichloroethane to be 1.15 ppb in indoor air samples collected from residential areas from July 1995 to May 1997 (Bonanno et al. 2001).

Table 6-3 was not in the package

Levels of 1,1,1-trichloroethane detected in water ways near sources of emissions such as industrial waste water, hazardous waste sites, and spill locations are usually <1 ppb. Drinking water from surface or

groundwater sources contained 1,1,1-trichloroethane concentrations of 0.01–3.5 ppb (Table 6-2). Limited monitoring data are available for the presence of 1,1,1-trichloroethane in soil. 1,1,1-Trichloroethane is expected to rapidly volatilize from soil and to leach through soil.

Table 6-2 was not found in the packag

Environmental exposures of humans to 1,1,1-trichloroethane have been correlated with levels of parent compound and 1,1,1-trichloroethane metabolites (trichloroethanol and trichloracetic acid) in expired air, blood, and urine (Hartwell et al. 1987a; Monster 1986; Wallace et al. 1982, 1984b, 1985, 1987a, 1987b, 1987c). The appearance of trichloroacetic acid in urine is not unique to 1,1,1-trichloroethane, as it has also been identified as a urinary metabolite of trichloroethylene and tetrachloroethylene (Monster 1988). If exposure is known to be solely to 1,1,1-trichloroethane, trichloroacetic acid levels in the urine may be a useful biomarker of exposure, because of the relatively long half-life of trichloroacetic acid. However, the length of time between 1,1,1-trichloroethane exposure and the measurement of breath, blood, or urine levels is critical to the accurate evaluation of the magnitude of exposure. Up to 90% of the 1,1,1-trichloroethane absorbed by any route is rapidly excreted unchanged in the expired air (Monster et al. 1979; Morgan et al. 1970, 1972b; Nolan et al. 1984; Stewart et al. 1961, 1969). Most of the remaining 10% is accounted for as the urinary metabolites trichloroethanol and trichloroacetic acid.

2.2 SUMMARY OF HEALTH EFFECTS

1,1,1-Trichloroethane is one of many solvents inhaled by some people to alter mood or consciousness. Available human and animal data indicate that the central nervous system is the most sensitive target for 1,1,1-trichloroethane toxicity. Clinical signs of toxicity associated with human exposure to large quantities of 1,1,1-trichloroethane include central nervous system depression, hypotension, cardiac arrhythmia, diarrhea and vomiting, mild hepatic effects, and dermal and ocular irritation. Deaths of persons exposed to high concentrations have been attributed to cardiac arrhythmia and respiratory failure secondary to central nervous system depression. Lower-level exposure to 1,1,1-trichloroethane may result in more subtle neurological effects such as impaired performance in tests designed to measure variables such as manual dexterity, eye-hand coordination, perceptual speed, and reaction time (Gamberale and Hultengren 1973; Mackay et al. 1987). Mild hepatotoxicity has been demonstrated in some animals exposed to relatively large quantities of 1,1,1-trichloroethane. Mild developmental effects induced by high level exposure of animals have not been verified in humans. Available data are inadequate to determine the carcinogenicity of 1,1,1-trichloroethane. The EPA has classified 1,1,1-tri-

been reported in humans exposed to high levels of 1,1,1-trichloroethane by inhalation or ingestion (Halevy et al. 1980; Hodgson et al. 1989; Stewart and Andrews 1966). Elevated serum LDH, gamma-glutamyl transpeptidase (GGT), SGOT, and glutamic pyruvic transaminase (SGPT), and pathologic signs of progressive liver disease were noted in a patient who was occupationally exposed to 1,1,1-trichloroethane for several years (Cohen and Frank 1994). Removal of the patient from exposure resulted in improvement of the impaired liver function. Mild hepatic changes have also been found ~~by~~ in the liver biopsy ~~in~~ of exposed individuals and at autopsy in individuals who died after acute inhalation exposure to high concentrations of 1,1,1-trichloroethane (Caplan et al. 1976; Halevy et al. 1980; Hall and Hine 1966; Hodgson et al. 1989). Animals studies indicate that exposure to relatively high 1,1,1-trichloroethane concentrations in air (≥1,000 ppm) or high oral doses (≥1,334 mg/kg) are required to produce liver injury (Adams et al. 1950; Bruckner et al. 2001; Calhoun et al. 1981; McNutt et al. 1975; NTP 1996, 2000; Torkelson et al. 1958; Tyson et al. 1983). Effects observed in animals include necrosis, fatty change, increased liver weight, and changes in liver and serum enzyme levels. These effects are reversible and subside after termination of exposure (in the case of necrosis, hepatocytes in the proximity of the killed cells proliferate and replace them).

Developmental Effects. Developmental effects in humans exposed to 1,1,1-trichloroethane have not been observed. Epidemiology studies found no relationship between adverse pregnancy outcomes and maternal exposure to 1,1,1-trichloroethane (Deane et al. 1989; Lindbohm et al. 1990; Swan et al. 1989; Taskinen et al. 1989; Windham et al. 1991; Wrensch et al. 1990a, 1990b). Minor embryotoxic effects were observed in rats and rabbits after inhalation exposure to high concentrations of 1,1,1-trichloroethane (BRRC 1987a, 1987b; York et al. 1982). Effects included decreased fetal weights, increased minor soft tissue and skeletal anomalies, and delayed ossification. Exposure of pregnant mice to 1,1,1-trichloroethane at a concentration of 2,000 ppm for 17 hours/day on gestation days 12–17 resulted in significantly reduced postnatal pup weights, overt developmental delays (pinnae detachment, incisor eruption, eye opening), and impaired performance in behavioral tests (righting reflex, forelimb grip strength, negative geotaxis, inverted screen climbing) (Jones et al. 1996). In a similar study of pregnant rats that were exposed to 7,000 ppm of 1,1,1-trichloroethane 3 times/day for 60 minutes on gestation days 13–19, two of nine litters were completely resorbed and significant increases in gestation length were noted. Developmental effects included increased mortality at birth, decreased litter weight, and significant deficits in coordination, muscle strength, and spontaneous motor activity (Coleman et al. 1999). The developmental defects reported in three of these studies (BRRC 1987a, 1987b; Coleman et al. 1999) may have been associated with significant maternal toxicity. Neither an inhalation study using a lower,

although still high, concentration (Schwetz et al. 1975) nor drinking water studies (George et al. 1989; Lane et al. 1982; NTP 1988a, 1988b) revealed any developmental effects. Furthermore, a comprehensive study in which pregnant rats were gavaged with 1,1,1-trichloroethane during gestation and lactation found no neurobehavioral alterations in the pups tested up to 2 months of age (Dow Chemical 1993). Overall, 1,1,1-trichloroethane does not appear to be a significant developmental toxicant in animals. However, in view of the known neurological effects of 1,1,1-trichloroethane in humans and animals, additional developmental studies that examine neurological end points would be an important component of a complete investigation of 1,1,1-trichloroethane's potential developmental toxicity in humans.

Cancer. A relationship between exposure to 1,1,1-trichloroethane and cancer in humans has not been established. Among animals, no effects were found in a well-designed inhalation study at exposure levels ≤1,500 ppm (Quast et al. 1988). The results of an oral study indicate that 1,1,1-trichloroethane may have increased the occurrence of immunoblastic lymphosarcoma in rats; however, the biological and statistical significance of these results are questionable because of the study design limitations (Maltoni et al. 1986). The results of another oral (gavage) cancer bioassay (NCI 1977) were negative, but high early mortality in treated animals in this study made these results questionable.

Information is also limited on the role of 1,1,1-trichloroethane metabolites in the parent compound's toxicity. Reactive metabolites are important in the carcinogenicity of other chloroethanes (i.e., 1,1,2,2-tetrachloroethane). Binding to DNA, which is correlated with carcinogenicity in chlorinated ethanes (Lattanzi et al. 1988), was weak in an *in vivo* test (Turina et al. 1986). Even weak binding, however, indicates the potential to interact with DNA. Cell biotransformation tests were positive for this chemical (Daniel and Dehnel 1981; Hatch et al. 1982, 1983; Milman et al. 1988; Price et al. 1978; Tu et al. 1985). The results of these assays may have been confounded by the presence of stabilizing agents, however. Two of the common stabilizing additives in commercial formulations of 1,1,1-trichloroethane are 1,2-epoxybutane (butylene oxide) and 1,4-dioxane (diethylene dioxide). Both stabilizers have been identified as animal carcinogens (NTP 1989a). At this time, it does not appear that 1,1,1-trichloroethane exposure poses a clear cancer risk in animals; however, as discussed above, the limitations of the available studies prevent a definitive assessment of the risk of cancer in humans exposed to the compound. Related to potential exposures near NPL hazardous waste sites, the risk appears to be of little significance.

reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

LSE (abbreviated on page 22, line 10)

3.2.1 Inhalation Exposure

3.2.1.1 Death

1,1,1-Trichloroethane is one of many solvents intentionally inhaled by some people to alter mood or consciousness. Solvent abuse of this type is associated with "sudden sniffing death" syndrome. In a survey of sudden sniffing deaths across the United States in the 1960s, 29 of the 110 deaths in the survey were attributed to inhalation of 1,1,1-trichloroethane (Bass 1970). Case reports of individuals who died following intentional inhalation of 1,1,1-trichloroethane are readily available (D'Costa and Gunasekera 1990; Droz et al. 1982; Guberan et al. 1976; Hall and Hine 1966; MacDougall et al. 1987; Ranson and Berry 1986; Travers 1974; Winek et al. 1997). 1,1,1-Trichloroethane is a widely used industrial solvent. Although mortality due to accidental exposure from its use as a solvent is not common, a number of cases have been reported (Caplan et al. 1976; Jones and Winter 1983; McCarthy and Jones 1983; Mercier 1977; Northfield 1981; Silverstein 1983; Stahl et al. 1969; Sullivan 1994).

Data from case reports and surveys are useful, but concomitant exposure to other chemicals cannot be ruled out, and exposure concentrations and durations are rarely known. Although the actual levels of exposure that produced death are not known for any of these cases, some investigators used simulations to estimate the fatal exposure concentrations. Droz et al. (1982) performed detailed simulations of two fatalities from intentional 1,1,1-trichloroethane inhalation. The lethal concentration of 1,1,1-trichloroethane was estimated to be between 6,000 and 14,000 ppm in one case and between 10,000 and 20,000 ppm in the other. Simulation of the circumstances of deaths of two people exposed while using 1,1,1-trichloroethane as a solvent showed that concentrations ≤6,400 ppm may have been generated in one case (Jones and Winter 1983) and concentrations ≤9,000 ppm may have been generated in the other (Silverstein 1983). Northfield (1981) reported a case in which a worker, whose death was attributed to respiratory failure, may have been exposed to 1,1,1-trichloroethane concentrations of 6,000 ppm or higher, depending on distance from the source.

1,1,1-trichloroethane in both humans and animals progresses from subtle behavioral effects at low-to-moderate concentrations to unconsciousness at high concentrations. There is evidence to suggest that 1,1,1-trichloroethane does not produce permanent neurological effects in humans. A study in gerbils, however, has produced evidence of lasting physical damage to the nervous system (astrogliosis) following prolonged continuous exposure to low concentrations (210 ppm) of this chemical. More data are needed to determine whether these results/observations are relevant for determining human risk.

3.2.1.5 Reproductive Effects

Limited information is available regarding the reproductive toxicity of 1,1,1-trichloroethane in humans, and exposure levels have not been quantified. Taskinen et al. (1989) conducted a case-control epidemiology study to investigate the relationship between adverse pregnancy outcomes (spontaneous abortions and congenital malformations) and occupational exposure of fathers to organic solvents, including 1,1,1-trichloroethane, during spermatogenesis for the 80 days prior to conception. No relationship was found between exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes. An apparent decrease in fertility (as measured by number of menstrual cycles required for wife to become pregnant) was noted in Finnish male workers ~~with~~ expo~~sure~~ed to 1,1,1-trichloroethane, but the difference from controls was not statistically significant (Sallmén et al. 1998).

Studies in several animal species found no evidence that 1,1,1-trichloroethane has adverse reproductive effects. Histological examination of male and female reproductive tissues following acute-, intermediate-, and chronic-duration exposure to 1,1,1-trichloroethane revealed no exposure-related changes in rats, mice, or rabbits (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977); however, varying degrees of testicular degeneration were observed in male guinea pigs exposed to 5,000 ppm 1,1,1-trichloroethane for 45 days (Adams et al. 1950). One intermediate-duration study used blood chemistry analyses to determine reproductive effects. Continuous exposure to moderate levels of 1,1,1-trichloroethane vapor had no effect on butyrylcholinesterase activity in mice, which suggests that exposure did not have any effect on testosterone activity (Kjellstrand et al. 1985b). Testosterone appears to play a major role in regulating butyrylcholinesterase activity, and, although activity of this enzyme may change in the absence of an effect on testosterone, it is unlikely that an effect on testosterone levels would not be reflected by a change in butyrylcholinesterase activity.

The highest NOAEL values for developmental effects in each species are recorded in Table 3-2 and plotted in Figure 3-2. The weight of evidence in experimental animal studies suggests that 1,1,1-trichloroethane is not a developmental toxicant when administered orally; however, this conclusion is limited by the use of low doses in some of the studies. Epidemiology studies found no evidence that exposure to 1,1,1-trichloroethane was responsible for the cluster of adverse pregnancy outcomes in Santa Clara County, California.

3.2.2.7 Cancer

Isacson et al. (1985) investigated the relationship between the presence of organic chemicals, including 1,1,1-trichloroethane, in drinking water and the incidence of cancer in Iowa residents. The authors contrasted towns that had detectable quantities of 1,1,1-trichloroethane in the water supply with those that did not and found no difference in the incidence of bladder, colon, lung, rectum, breast, or prostate cancer in people over age 55. 1,1,1-Trichloroethane levels >0.1 μg/L (but unspecified) were detectable in this study. Assuming the average adult weighs 70 kg and drinks 2 liters of water per day, a concentration of 0.1 μg/L would produce a dose of approximately 0.000003 mg/kg/day. The authors concede that their data are not sensitive enough to support conclusions regarding the apparent lack of association between 1,1,1-trichloroethane in the water supply and cancer risk in humans. No other studies were located regarding risks of cancer in humans after oral exposure to 1,1,1-trichloroethane.

NCI (1977) conducted a bioassay for carcinogenicity of 1,1,1-trichloroethane in rats and mice. The test animals were exposed to high gavage doses of the chemical (750 or 1,500 mg/kg/day for rats and 2,807 or 5,615 mg/kg/day for mice) for 78 weeks. All animals were necropsied and the tissues were examined histologically. The incidence and type of neoplasms observed were similar to those seen in untreated controls. Vehicle controls were not used in this study. There was a significant dose-related decrease in survival of both rats and mice. Among rats, no males and only 2–4% females survived to the end of the experiment. Among mice, 22–30% of treated males and 26–46% of treated females survived. Because the high rate of early mortality may have lowered the incidence of late-appearing tumors, the authors did not consider this study an adequate test of 1,1,1-trichloroethane carcinogenicity in either species.

3.2.3.7 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to 1,1,1-trichloroethane.

3.3 GENOTOXICITY

The genotoxic effects of 1,1,1-trichloroethane have been studied extensively. The results are summarized in Tables 3-4 and 3-5. Although most tests of mutagenicity in the Ames *Salmonella* assay produced negative results, those conducted in a desiccator, to minimize evaporation and maximize exposure, were mostly positive (Gocke et al. 1981; Nestmann et al. 1980, 1984; Simmon et al. 1977). These results indicate that 1,1,1-trichloroethane may be mutagenic in *Salmonella*. The results were negative in other tests of genotoxicity in bacteria and fungi. 1,1,1-Trichloroethane is a relatively volatile compound; therefore, a high evaporation rate could result in lower doses reaching the microorganisms and thus affect the outcome of genotoxicity tests. This explanation may account for the largely negative results observed in tests with bacteria and fungi. On the other hand, many compounds more volatile than 1,1,1-trichloroethane are positive in these studies. A weakly positive result was obtained in a test for induction of deletions via intrachromosomal recombination in the yeast *Saccharomyces cerevisiae* (Brennan and Schiestl 1998).

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Most assays of genotoxicity in mammalian cells have been negative, but 1,1,1-trichloroethane did produce chromosomal aberrations in Chinese hamster ovary cells *in vitro* (Galloway et al. 1987). *In vivo* micronucleus tests for chromosomal aberrations were all negative (Gocke et al. 1981; Katz et al. 1981; Halogenated Solvents Industry Alliance 1990; Salamone et al. 1981; Tsuchimoto and Matter 1981). Positive or weakly positive results were reported in assays for unscheduled DNA synthesis in mouse hepatocytes (Milman et al. 1988); degranulation of endoplasmic reticulum, which measures the ability of a compound to displace polysomes from endoplasmic reticulum in rat hepatocytes *in vitro* (Fey et al. 1981); and formation of DNA adducts (binding of the compound to DNA) in mouse liver *in vivo* (Turina et al. 1986). Tests of cell transformation in rat embryo cells, hamster embryo cells, baby hamster kidney cells, and mouse BALB/c-3T3 cells were almost all positive (Daniel and Dehnel 1981; Hatch et al. 1982,

1983; Milman et al. 1988; Price et al. 1978; Tu et al. 1985). Cell transformation systems are believed to be similar to the process of neoplastic transformations.

Although 1,1,1-trichloroethane was mutagenic in a few assays with *Salmonella*, induced chromosomal aberrations in a Chinese hamster ovary cell assay, and was positive in most mammalian cell transformation assays, the existing genotoxicity data are largely negative. In addition, positive results may have been produced by stabilizers and not 1,1,1-trichloroethane itself. Therefore, a firm conclusion regarding the genotoxic potential of 1,1,1-trichloroethane in humans is not possible.

3.4 TOXICOKINETICS

Upon first exposure, 1,1,1-trichloroethane is rapidly and efficiently absorbed by the lung, skin (under conditions to prevent evaporation), and gastrointestinal tract of humans and animals. As the duration of inhalation exposure increases, the percentage of absorption decreases because steady-state levels are approached in the blood and tissues, and 1,1,1-trichloroethane is metabolized at a low rate. Animal studies have demonstrated that, once absorbed, 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, including to developing fetuses, with preferential distribution to fatty tissues. The predominant pathway of elimination of 1,1,1-trichloroethane in humans and animals, regardless of route of exposure, is exhalation of the unchanged compound. When exposure ceases, the compound is rapidly cleared from the body. In animal studies, only trace amounts of the compound remain in tissues within days of the termination of short-term exposure. (reference(s) should be given)

1,1,1-Trichloroethane is metabolized oxidatively, at low rates, to trichloroethanol and trichloroacetic acid by the cytochrome P-450 mixed-function oxidase system. These metabolites are excreted in the urine; other minor metabolites (carbon dioxide [CO_2] and acetylene) are excreted in expired air. (The acetylene is formed by reductive dechlorination of 1,1,1-trichloroethane under conditions of low oxygen supply.) provide reference(s) Experiments with animals and humans have demonstrated that only small fractions of absorbed 1,1,1-trichloroethane doses (<10%) are metabolized, regardless of the route of exposure. The toxicokinetic behavior of 1,1,1-trichloroethane has the same qualitative pattern in humans, rats, and mice; however, some quantitative differences among these species have been observed, including a higher blood:air partition coefficient and an increased rate of metabolism in mice compared with rats and humans. Physiologically-based pharmacokinetic models have been developed to describe the kinetic behavior of

trichloroethanol and trichloroacetic acid, collected for 70 hours postexposure represented approximately 2 and 0.5% of the 1,1,1-trichloroethane initially absorbed. In humans exposed to 35 or 350 ppm for 6 hours, >91% of absorbed 1,1,1-trichloroethane was excreted unchanged by the lungs, 5–6% was metabolized and excreted as trichloroethanol and trichloroacetic acid, and <1% remained in the body after 9 days (Nolan et al. 1984).

In rats and mice dosed by gavage with 1,1,1-trichloroethane in vegetable oil 5 days/week for 4 weeks, followed by a single dose of ^{14}C-labeled compound, 85.1 and 92.3% of the respective doses were recovered as unchanged compound in expired air; respective recovery percentages of metabolite fractions (48 hours after administration) in rats and mice were 0.9 and 2.0% as CO_2, 2.1 and 3.4% as metabolites in urine, and 1.2 and 0.7% as presumed metabolites remaining in the carcasses (Mitoma et al. 1985). Similarly, exhalation of unchanged compound was the predominant pathway for elimination of absorbed 1,1,1-trichloroethane, accounting for >90% of doses administered in drinking water studies with rats (Reitz et al. 1988) and in inhalation studies with rats and mice (Schumann et al. 1982a). Comparison of metabolic disposition in mice and rats indicated that mice metabolized 2–3 times more 1,1,1-trichloroethane on a body weight basis; however, in both species, metabolism was a dose-dependent, saturable process that represented a minor route of elimination (Schumann et al. 1982a, 1982b).

Analysis of urine following human and animal exposure to 1,1,1-trichloroethane identified trichloroethanol, trichloroethanol glucuronide, and trichloroacetic acid as major metabolites of 1,1,1-trichloroethane; CO_2, identified in exhaled breath, is the other major metabolite (Kawai et al. 1991; Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; Schumann et al. 1982a). Figure 3-3 illustrates a general metabolic scheme for 1,1,1-trichloroethane. The initial oxidation step is thought to be catalyzed by the microsomal cytochrome P-450 mixed-function oxidase system. In vitro reaction mixtures containing rat hepatic microsomes and nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) oxidize 1,1,1-trichloroethane to trichloroethanol. 1,1,1-Trichloroethane metabolism significantly increased when microsomes from rats pretreated with phenobarbital, an inducer of certain isozymes of cytochrome P-450, were used. This finding provides supporting evidence of the involvement of this enzyme system in the metabolism, albeit limited, of 1,1,1-trichloroethane (Ivanetich and Van den Honert 1981; Koizumi et al. 1983). The pathway for conversion of trichloroethanol to trichloroacetic acid presumably involves the intermediate formation of chloral hydrate and may involve alcohol and aldehyde dehydrogenases or cytochrome P-450 mixed-function oxidases (Casciola and Ivanetich 1984; Ivanetich and Van den Honert 1981). Although trichloroacetic acid or chloral hydrate were not detected as in vitro

(This Fig. is not in the package)

metabolic products of 1,1,1-trichloroethane with rat hepatic microsomal cytochrome P-450 preparations (Ivanetich and Van den Honert 1981; Koizumi et al. 1983), in vitro production of chloral hydrate from 1,1,1-trichloroethane was demonstrated in reaction mixtures containing rat nuclei cytochrome P-450 preparations (Casciola and Ivanetich 1984).

In vivo and *in vitro* evidence from rat experiments suggests that, under conditions of low oxygen supply, 1,1,1-trichloroethane can be reductively dechlorinated, to a limited extent, to dechlorinated radical intermediates and eventually to acetylene (Durk et al. 1992); in these experiments, exhaled acetylene accounted for <1% of metabolized 1,1,1-trichloroethane. The reductive dechlorination of 1,1,1-trichloroethane appears to be mediated by cytochrome P-450, since putative induction by phenobarbital treatment accelerated the in vitro and in vivo metabolic formation of acetylene. The reductive metabolic pathway is not indicated in Figure 3-3, because it apparently represents a very minor 1,1,1-trichloroethane metabolic pathway.

Repeated exposure of mice and rats to 1,1,1-trichloroethane apparently does not increase the relative importance of metabolism to the *in vivo* disposition of the compound (Schumann et al. 1982b), even though another research group reported that hepatic microsomes from rats exposed continuously for 10 days to 800 ppm of 1,1,1-trichloroethane displayed greater in vitro enzymatic activities for 1,1,1-trichloroethane oxidation than microsomes from fresh-air controls (Koizumi et al. 1983). Schumann et al. (1982b) found that repeated exposure of rats or mice to 1,500 ppm unlabeled 1,1,1-trichloroethane for 16 months did not alter the routes of excretion, the extent of metabolism, or the concentration of radioactivity in tissues after a 6-hour inhalation exposure to 1,500 ppm [$^{2-14}$C]-1,1,1-trichloroethane, [2-^{14}C] compared with age-matched animals subjected to single 6-hour exposures. In general, studies regarding the effects of 1,1,1-trichloroethane on hepatic enzyme induction are inconclusive. Although Koizumi et al. (1983) and others (Bruckner et al. 2001; Fuller et al. 1970; Lal and Shah 1970) reported that 1,1,1-trichloroethane induced hepatic cytochrome P-450 enzyme levels in rats, others observed no effects (Toftgaard et al. 1981; Wang et al. 1996) or inhibitory effects (Nakahama et al. 2000; Savolainen et al. 1977) in rats exposed to 1,1,1-trichloroethane.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

After acute exposure, most inhaled 1,1,1-trichloroethane is rapidly excreted unchanged in expired air of humans and animals. Within 1 hour of administration, humans exhaled 44% of the radioactivity they had inhaled from a single breath of radiolabeled 1,1,1-trichloroethane (Morgan et al. 1970). Humans exposed to 70 or 145 ppm for 4 hours exhaled 60–80% of inhaled 1,1,1-trichloroethane unchanged during a 150-hour period after exposure (Monster et al. 1979). Other humans exposed to 35 or 350 ppm for 6 hours exhaled >91% of absorbed 1,1,1-trichloroethane as the unchanged compound within 9 days of exposure (Nolan et al. 1984). Similar observations were made in studies of rats (Ikeda and Ohtsuji 1972; Schumann et al. 1982a, 1982b), mice (Schumann et al. 1982a, 1982b), and anesthetized dogs (Hobara et al. 1982). Nolan et al. (1984) described the temporal elimination pattern for 1,1,1-trichloroethane in blood and expired air of humans as "triexponential" and estimated half-lives of 44 minutes, 5.7 hours, and 53 hours for the initial, intermediate, and terminal phases, respectively. Raymer et al. (1991) used a two-compartment model to fit experimental observations of the temporal decrease in 1,1,1-trichloroethane concentrations in human breath samples collected for 4 hours after exposure to contaminated atmospheres; elimination half-lives ranged from 0.00 to 0.17 hours for the first compartment and from 1.80 to 6.08 hours for the second compartment. check this value ?

Exhalation of CO_2 and urinary excretion of metabolites (trichloroethanol and trichloroacetic acid) represent minor elimination pathways for inhaled 1,1,1-trichloroethane. Nevertheless, observed correlations between urinary concentrations of 1,1,1-trichloroethane metabolites and exposure concentrations indicate that urine analysis may be a useful method of exposure assessment (Caperos et al. 1982; Ghittori et al. 1987; Imbriani et al. 1988; Kawai et al. 1991; Mizunuma et al. 1995; Seki et al. 1975). Estimated half-lives for the elimination of trichloroethanol and trichloroacetic acid from human blood after inhalation exposures to 1,1,1-trichloroethane were 10–27 hours for trichloroethanol and 70–85 hours for trichloroacetic acid (Monster et al. 1979; Nolan et al. 1984). The long half-life of trichloroacetic acid is due to binding of this metabolite to plasma proteins. Daily occupational exposure to 1,1,1-trichloroethane progressively increased urinary metabolite levels during the workweek, while levels decreased over the weekend (Seki et al. 1975). This observation is consistent with observations of the rapid clearance of 1,1,1-trichloroethane and its metabolites from animal tissues after inhalation exposure (Dallas et al. 1989; Holmberg et al. 1977; Schumann et al. 1982a, 1982b; Takahara 1986a).

biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

Literature search revealed a PBPK model for 1,1,1-trichloroethane in rats, mice, and humans (Reitz et al. 1988) that was based on a four-compartment model developed for styrene (Ramsey and Andersen 1984). Adaptations of the Reitz et al. (1988) model were presented by others (Bogen and Hall 1989; Dobrev et al. 2001, 2002; Poet et al. 2000).

Reitz et al. (1988) 1,1,1-Trichloroethane Biokinetics Model

Description of the Model. Reitz et al. (1998) developed a four-compartment model for rats, mice, and humans, which predicts the behavior of inhaled 1,1,1-trichloroethane in liver, rapidly perfused tissue, slowly perfused tissue, and fat. Tissue volumes and blood and airflow rates employed in the model are listed in Table 3-6. The percentage of cardiac output directed to the fat compartments was adjusted for interspecies differences in fat content. Tissue:blood partition coefficients (Table 3-6) were used to calculate the 1,1,1-trichloroethane concentration in venous blood leaving the tissue and were estimated

Table 3-6 is not provided in the package

with rat blood, liver, fat, and muscle tissue using a vial-equilibration technique. Blood:air partition coefficients were determined with human and mouse blood. Metabolism was restricted to the liver and was described by Michaelis-Menten kinetics. Metabolic kinetic constants (Vmax and Km; Table 3-6) were estimated by optimization of the model with 1,1,1-trichloroethane blood concentration data for rats exposed by inhalation to 150 or 1,500 ppm for 6 hours (Schumann et al. 1982a). The model was designed to be applicable to exposures via drinking water, bolus gavage, and intravenous administration as well. For drinking water exposures, uptake of 1,1,1-trichloroethane from the gastrointestinal tract and transfer to the liver was assumed to follow zero-order kinetics. Simulation of gavage administration assumed first-order absorption from the gastrointestinal tract, with a rate constant of 1.25/hour. Both oral (drinking water or gavage) and intravenous administration assumed direct transfer to the liver.

Table 3-6 is not in the package

Validation of the Model. Predictions based on the model were compared to observed values for experimentally-determined end exposure 1,1,1-trichloroethane blood levels, amount of 1,1,1-trichloroethane metabolized, and concentrations of 1,1,1-trichloroethane in fat or liver ~~in~~ of rats and mice following exposure via drinking water or inhalation, and on observed values of the amount of 1,1,1-trichloroethane metabolized in human volunteers following inhalation exposure. Model predictions agreed reasonably well with the empirical observations (Reitz et al. 1988).

Bogen and Hall (1989) adapted the Reitz et al. (1988) rat model to gerbils using a scaling factor and presented a five-compartment model (liver, richly perfused tissues, poorly perfused tissues, fat, and skin) for a 70-kg adult male subject using reference values from EPA (1988m) for tissue-specific volumes, blood perfusion rates, and cardiac output. Values for skin were assumed to be 6% of reference values for poorly perfused tissues. Poet et al. (2000) modified the PBPK model of Reitz et al. (1988) to include a separate skin compartment. Dobrev et al. (2001, 2002) presented a model for mixed exposures to trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane.

Fisher et al. (1997) modeled the excretion of 1,1,1-trichlorethane (and other volatile organic chemicals) via the breast milk. Model simulations predicted a low degree (<1%) of lactational transfer of 1,1,1-trichloroethane. However, model predictions were not validated with empirical data.

cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,1,1-trichloroethane are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 "Populations That Are Unusually Susceptible".

3.8.1 Biomarkers Used to Identify or Quantify Exposure to 1,1,1-Trichloroethane

Environmental levels of 1,1,1-trichloroethane have been correlated with levels in expired air, blood, and urine. After extensive studies, a significant correlation was observed between the environmental exposure of humans to 1,1,1-trichloroethane and levels of the chemical in expired air in various U.S. locations during various seasons (Hartwell et al. 1987a; Wallace et al. 1982, 1984b, 1985, 1987a, 1987b, 1987c). Levels of 1,1,1-trichloroethane and its metabolites, trichloroethanol and trichloroacetic acid, have been quantified in the blood, expired air, and urine of workers exposed to 50 ppm 1,1,1-trichloroethane for 1 week (Monster 1986). Immediately following exposure, urine levels of trichloroethane and trichloroacetic acid were 4.9 and 2.5 mg/g creatinine, respectively. At 5–15 minutes after exposure, 1,1,1-trichloroethane levels in the blood and expired air were 0.9 mg/L and 210 mg/m^3, respectively. The blood levels of trichloroethanol and trichloroacetic acid were 0.16 and 2.3 mg/L, respectively. For comparison, the baseline level of 1,1,1-trichloroethane in the blood of unexposed, normal subjects was 0.0002 mg/L (range <0.0001–0.0034 mg/L) and the blood level of trichloroacetic acid was 0.0214 mg/L (Hajimiragha et al. 1986). Studies of 1,1,1-trichloroethane levels in expired air or its metabolites in the urine have established a linear correlation between urinary trichloroethanol concentrations and environmental 1,1,1-trichloroethane levels or 1,1,1-trichloroethane levels absorbed through the lungs (Ghittori et al. 1987; Imbriani et al. 1988; Mizunuma et al. 1995; Monster 1986; Pezzagno et al. 1986; Seki et al. 1975; Stewart et al. 1961). Data from Imbriani et al. (1988) are presented in Figure 3-5. Figure 3-5 is not in the package

adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,1,1-trichloroethane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of 1,1,1-Trichloroethane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1,1-trichloroethane are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,1,1-trichloroethane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Not found in the package

Several case studies have documented the lethality of high concentrations of inhaled 1,1,1-trichloroethane. Experimental studies, as well as case reports, have reported on acute systemic and neurological effects. Chronic systemic, neurological, developmental, and reproductive effects have been investigated in epidemiology studies. Health effects caused by other routes of administration have not been as well studied in humans. One case study regarding oral exposure to 1,1,1-trichloroethane reported acute systemic effects and investigated potential neurological effects. Developmental effects and cancer from exposure to drinking water were investigated by epidemiology studies. The effects of dermal exposure

conclusions regarding the health effects of 1,1,1-trichloroethane exposure. More extensive studies might provide a definitive assessment of the health hazards of chronic 1,1,1-trichloroethane exposure in humans, especially for occupationally exposed populations. If such effects are identified, human dosimetry studies may be able to correlate 1,1,1-trichloroethane levels in human tissues or fluids with chronic health effects. The usefulness of such studies on individuals living near hazardous waste sites is questionable since exposure is relatively low and the half-life of 1,1,1-trichloroethane and its metabolites too short. Acute experimental studies in humans have established inhalation exposure levels associated with acute neurological effects. Subpopulations potentially exposed to 1,1,1-trichloroethane include people residing near hazardous waste sites where the chemical is stored, people who encounter it in the workplace (either in its manufacture or application), and people who use household products that contain it. It should be mentioned, however, that as a result of Title VI of the Clean Air Act, potential human exposure to 1,1,1-trichloroethane is expected to be gradually reduced (see Chapter 6).

Biomarkers of Exposure and Effect.

Exposure. Known biomarkers of 1,1,1-trichloroethane exposure include blood, breath, and urine levels of the chemical and its two major metabolites, trichloroethanol and trichloroacetic acid. Metabolism of trichloroethylene and perchloroethylene also produces trichloroethanol and trichloroacetic acid; therefore, these metabolites are not unique to 1,1,1-trichloroethane (Monster 1988). Environmental 1,1,1-trichloroethane levels are significantly correlated with ~~the~~ levels in blood, breath, and urine (Hartwell et al. 1987a; Mizunuma et al. 1995; Monster 1986; Wallace et al. 1982, 1984b, 1985, 1987a, 1987b, 1987c). 1,1,1-Trichloroethane is rapidly cleared from the body after exposure (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984; Stewart et al. 1961). The two metabolites have a much longer half-life in the body than the parent compound. Therefore, 1,1,1-trichloroethane levels in the blood, breath, and urine may be used as biomarkers only if they are measured during or shortly after exposure. The two metabolites are more useful as biomarkers for a somewhat longer period after exposure. Because 1,1,1-trichloroethane's half-life in the body is short, and because hematological profiles and clinical chemistry parameters are not usually affected, the further development of biomarkers based on easily-obtained biological fluids may not be useful.

Effect. No specific biomarkers of effect for 1,1,1-trichloroethane were located in the literature. The central nervous system is apparently the most sensitive organ in humans and animals, and neurotoxicity (decreased psychomotor performance, ataxia, and unconsciousness) is observed after short-term high-

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of 1,1,1-trichloroethane is located in Table 4-1.

Tables 4-1 and 4-2 are not in the package

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of 1,1,1-trichloroethane is located in Table 4-2.

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

5.1 PRODUCTION

Two chemical companies are listed as domestic manufacturers in 2003 (SRI 2003): Vulcan Materials Co. Chemicals Division in Geismer, Louisiana and PPG Industries in Lakes Charles, Louisiana. The estimated total production capacity at each of the facilities in 1994 (in millions of pounds) is 350 for PPG's plant in Lake Charles, Louisiana and 160 for Vulcan's plant in Geismar, Louisiana (estimated total capacity of 510 million pounds as of April 1, 2003) (SRI 2003).

The total production volumes of 1,1,1-trichloroethane fell from 720 million pounds in 1992 to 450 million pounds in 1993 (CMR 1995). The demand for 1,1,1-trichloroethane was projected to decline at the rate of -10% per year through 1999 (CMR 1995). According to the 1990 amendments to the Clean Air Act and the Montreal Protocol, U.S. production of 1,1,1-trichloroethane will be cut incrementally until the proposed phase-out scheduled to occur by January 2002 (EPA 2004m). During the period beginning on January 1, 2002 and ending on January 1, 2005, production of limited amounts of 1,1,1-trichloroethane may be authorized by the Administrator for use in essential applications. Despite the proposed phase-out, 1,1,1-trichloroethane was still being manufactured in the United States in 2002 in a production volume range of >100 to <500 million pounds for 2002 (Inventory Update Rule 2004)

Besides the above producers of 1,1,1-trichloroethane, Table 5-1 reports the number of facilities in each state that manufacture and process 1,1,1-trichloroethane, the intended use of the product, and the range of maximum amounts of 1,1,1-trichloroethane stored on site. The data reported in Table 5-1 are derived from the Toxics Release Inventory (TRI) (TRI01 2004). Only certain types of facilities were required to report to the TRI databank of EPA. Hence, this is not an exhaustive list.

Table 5-1 is not in the package

The most common method for industrial preparation of 1,1,1-trichloroethane is the reaction of hydrochloric acid with vinyl chloride (obtained from 1,2-dichloroethane) to obtain 1,1-dichloroethane, followed by either thermal or photochemical chlorination. Other methods include the catalyzed addition of hydrogen chloride to 1,1-dichloroethylene, and the direct chlorination of ethane itself, followed by separation from the other products produced (Archer 1979). Commercial grades of 1,1,1-trichloroethane

boards, generators, switchgears, semiconductors, high vacuum equipment, fabrics, and wigs. It was also used for on-site cleaning of printing presses, food packaging machinery, and molds. 1,1,1-Trichloro- ethane is also used as a chemical intermediate in the production of hydrofluorocarbons and vinyl chloride. It was formerly used as a food and grain fumigant (Archer 1979; Aviado et al. 1976, 1980; Budavari 1989; Sax and Lewis 1987; Stewart 1983; WHO 1992).

chloro ? see page 110, line 19

1,1,1-Trichloroethane was used extensively in household products. In a "shopping basket" survey, 1,1,1-trichloroethane was found in 216 of 1,159 common household products chosen as likely to contain solvents at concentrations >0.1% by weight (Sack et al. 1992). In a similar study, 1,1,1-trichloroethane was found in 32 of 67 categories (1,026 brands sampled) of common household products at concentrations >1% by weight; trace amounts were listed in all 67 categories (EPA 1987; Maklan et al. 1987). Some of the several commonly used household items that may contain 1,1,1-trichloroethane are shown in Table 5-2. 1,1,1-Trichloroethane is emitted during use of items prevalent in the average home (Pleil and Whiton 1990; Wallace et al. 1987b).

5.4 DISPOSAL

1,1,1-Trichloroethane has been identified as a hazardous waste by EPA, and disposal of this waste is regulated under the Federal Resource Conservation and Recovery Act (RCRA). Specific information regarding federal regulations on 1,1,1-trichloroethane disposal on land, in municipal solid waste landfills, in incinerators, and during underground injection is available in the Code of Federal Regulations (EPA 1992a, 1992b, 1992c, 1992d). Disposal of 1,1,1-trichloroethane can be accomplished through its destruction in a high temperature incinerator equipped with a hydrochloric acid scrubber. The destruction and removal efficiency (DRE) for 1,1,1-trichloroethane in hazardous wastes must attain 99.99% (Carroll et al. 1992). Potential methods of incineration include liquid injection, rotary kiln, and fluidized bed incineration (Carroll et al. 1992; HSDB 2004). Product residues and sorbent media may be packaged in a 17H epoxy-lined drum, encapsulated in an organic polyester resin, and disposed of at an approved EPA disposal site (OHM/TADS 1992). Other methods that have shown promise for the destruction of 1,1,1-trichloroethane are homogeneous sonochemical treatment for aqueous wastes (Cheung et al. 1991) and a combination of ozonation and ultraviolet treatment for groundwater (Kusakabe et al. 1991). From a laboratory feasibility study, it was concluded that the in situ biodegradation of 1,1,1-trichloroethane in soils by methane-oxidizing bacteria was not a viable bioremediation method (Broholm et al. 1991).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

1,1,1-Trichloroethane has been identified in at least 809 of the 1,647 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). However, the number of sites evaluated for 1,1,1-trichloroethane is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 804 are located within the United States, 3 are located in the Commonwealth of Puerto Rico (not shown), 1 is located in the Virgin Islands (not shown), and 1 is located in Guam (not shown).

This Figure 6-1 is not in the packet

1,1,1-Trichloroethane is a synthetic compound that was released to the environment by human industrial activity. It was released to the environment by process and fugitive emissions during its manufacture, formulation, and use in both consumer and industrial products. Because 1,1,1-trichloroethane is volatile and was used as a solvent in many products, it was most frequently found in the atmosphere due to volatilization during production and use. Under the Clean Air Act as amended in 1990, all production and use of 1,1,1-trichloroethane was scheduled to cease as of January 1, 2002. 1,1,1-Trichloroethaene may still be used for essential applications such as medical devices and aviation safety (for the testing of metal fatigue and corrosion of existing airplane engines and other parts susceptible to corrosion) until January 1, 2005. Despite the proposed phase-out, 1,1,1-trichloroethane was still being manufactured in the United States in 2002 in a production volume range of >100 ~~K~~500 million pounds. More current production data are not yet available and therefore, it is unclear what stage the phase-out is in at this time.

1,1,1-Trichloroethane is no longer used in common household products. The current likelihood of the exposure of general population to 1,1,1-trichloroethane is remote. Possible routes of exposure to 1,1,1-trichloroethane were inhalation, dermal contact, or through the ingestion of either contaminated water or food. Exposure by inhalation was expected to predominate. The general population was exposed to 1,1,1-trichloroethane because of its prevalence in common household products. Indoor air concentrations were determined to be greater than nearby outdoor concentrations, probably as a result of its presence in a myriad of consumer products in the past. Occupational exposure to 1,1,1-trichloroethane could occur by inhalation or dermal contact during its manufacture and formulation, during its use as a cleaner of manufactured components, and during the application of the numerous paints, resins,

2001 are reported in the Toxics Release Inventory (TRI) and listed in Table 6-1 (TRI01 2004). According to TRI01 (2004), an estimated total of 206,859 pounds of 1,1,1-trichloroethane, amounting to 98.4% of the total environmental release, was discharged to the air from manufacturing and processing facilities in the United States in 2001. **The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.** However, a comparison of TRI data for 1992 and 2001 (115 million pounds and 206,859 pounds, respectively) shows that the nationwide emission of 1,1,1-trichloroethane in the atmosphere has decreased by 99.8% during this period. A 36% reduction in atmospheric emissions was observed in Irvine, California, from 1989 to 1990 (Brown and Hart 1992). Most processes that use 1,1,1-trichloroethane result in some fugitive emissions. For example, the release of 1,1,1-trichloroethane from an industrial solvent recycling facility was 16.7% of the throughput (Balfour et al. 1985).

6.2.2 Water

1,1,1-Trichloroethane can be released to surface water from the waste water of industries in any of the numerous industrial classifications that used or produced this compound. The STORET database for values registered in the years 1980–1988 shows that 1,1,1-trichloroethane tested positive in 12% of effluent samples with maximum, median, and mean concentrations of 6,500, 8.0, and 171 mg/L, respectively (STORET 1988). 1,1,1-Trichloroethane releases in water, including release to publicly owned treatment works (POTW), from facilities in each state in the United States that manufactured or processed 1,1,1-trichloroethane during 2001 are reported in Table 6-1 (TRI01 2004). According to TRI01 (2004), 0.01% of the total 1,1,1-trichloroethane environmental release was discharged to environmental waters from manufacturing and processing facilities in the United States in 2001. **The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.** Higher concentrations of 1,1,1-trichloroethane have been found in surface waters near known industrial sources, such as effluent outfalls or disposal sites, compared to the levels found upstream from these sources (see Table 6-2) (Dreisch et al. 1980; Hall 1984; Kaiser and Comba 1986; Kaiser et al. 1983; Wakeham et al. 1983a).

1,1,1-Trichloroethane has been found in samples from four U.S. cities measured in the National Urban Runoff Program (Cole et al. 1984). 1,1,1-Trichloroethane has been found in the effluent from water treatment plants and municipal waste water (Comba and Kaiser 1985; Corsi et al. 1987; DeWees et al.

1992; Feiler et al. 1979; Lue-Hing et al. 1981; McCarty and Reinhard 1980; Namkung and Rittman 1987; Otson 1987; Pincince 1988; Rogers et al. 1987; Vancil et al. 1991; Young 1978; Young et al. 1983).

1,1,1-Trichloroethane can enter groundwater from various sources. Contamination as a result of industrial activity has occurred (Dever 1986; Hall 1984). Leachate from landfills has percolated into groundwater (Barker 1987; Plumb 1987). The measured soil sorption coefficient (K_{oc}) value of 2.02 (Chiou et al. 1980; Gossett 1987) suggests that 1,1,1-trichloroethane released to soil can leach into groundwater. Measurements of 1,1,1-trichloroethane in drinking water from probability-based population studies (Wallace et al. 1984a, 1987a, 1988), indicate the potential for exposure from drinking water.

6.2.3 Soil

1,1,1-Trichloroethane release on land, including underground injection, from facilities in each state in the United States that manufactured or processed 1,1,1-trichloroethane during 2001 are reported in Table 6-1 (TRI01 2004). According to TRI01 (2004), an estimated total of 169 pounds of 1,1,1-trichloroethane, amounting to 0.08% of the total environmental release, was discharged to the land from manufacturing and processing facilities in the United States in 2001. **The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.**

Underlined Tables are not in the package

Data on soil contamination by 1,1,1-trichloroethane are lacking in the literature, which is what one would expect based on the TRI01 (2004) data given in Table 6-1. Contamination of soil is possible by direct application of insecticides and rodenticides that contain 1,1,1-trichloroethane as a solvent. Land application of sewage sludge at typical application rates may slightly elevate the level of 1,1,1-trichloroethane in agricultural soil, but the level is not expected to be of environmental concern in the majority of cases (Wilson et al. 1994). The most likely routes for soil contamination are through accidental spills, the contamination of soil by landfill leachates, leaching of contaminated surface waters from treatment/storage lagoons, wet deposition, and possibly by the percolation of contaminated rainwater through soil.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

1,1,1-Trichloroethane is a volatile organic compound with moderate water solubility (1,500 mg/L at 25 °C) (Horvath 1982). The experimental Henry's law constants measured for this compound range from 6.3×10^{-3} to 17.2×10^{-3} atm m^3/mol at 25 °C (Chiou et al. 1980; Gossett 1987; Tse et al. 1992); this suggests that volatilization from water should be the dominant fate process. Volatilization of 1,1,1-trichloroethane from water has readily occurred in the laboratory, in the field, and during waste water treatment (Dilling 1977; Dilling et al. 1975; Kincannon et al. 1983b; Piwoni et al. 1986; Wakeham et al. 1983b). Volatilization of 1,1,1-trichloroethane also has occurred from soil and from the groundwater of unconfined aquifers to the soil (Kreamer 1984; Piwoni et al. 1986).

Based on the experimental values for the log octanol/water partition coefficient (K_{ow}), 2.49 (Hansch and Leo 1985), and log K_{oc}, in the range of 2.02–2.26 (Chiou et al. 1979; Friesel et al. 1984; Park and Lee 1993), 1,1,1-trichloroethane would be expected to show high mobility in soil and readily leach into groundwater (Lyman et al. 1990; Swann et al. 1983). In surface waters, 1,1,1-trichloroethane would not be expected to show appreciable adsorption to sediment or suspended organic material. An experimental bioconcentration factor (BCF) of 9 (bluegill sunfish) has been determined for 1,1,1-trichloroethane (Barrows et al. 1980), suggesting that in fish and other aquatic organisms, uptake from water should not be an important fate process.

1,1,1-Trichloroethane has a vapor pressure of 123 mm Hg at 20 °C (see Table 4-2), which means that it exists in the vapor phase in the atmosphere (Eisenreich et al. 1983). Since this compound has moderate water solubility (see Table 4-2), vapor phase 1,1,1-trichloroethane will be removed from the air via washout by rain and transported to the terrestrial surface. It has been identified in rainwater (Jung et al. 1992; Kawamura and Kaplan 1983; Pluemacher and Renner 1993; Rasmussen et al. 1983). 1,1,1-Trichloroethane removed by rain water would be expected to re-volatilize rapidly to the atmosphere. Because of its long half-life of ≈4 years in the atmosphere (see Section 6.3.2.1), tropospheric 1,1,1-trichloroethane will be transported to the stratosphere, where it will participate in the destruction of the ozone layer. It will also undergo long-distance transport from its sources of emissions to other remote and rural sites. This is confirmed by the detection of this synthetic chemical in forest areas of Northern and Southern Europe and in remote sites (Ciccioli et al. 1993).

not found in the package

6.3.2 Transformation and Degradation

6.3.2.1 Air

The dominant atmospheric fate process for 1,1,1-trichloroethane is predicted to be degradation by interaction with photochemically-produced hydroxyl radicals. Earlier experimental rate constants for this gas-phase reaction ranged from 2.8×10^{-14} to 1.06×10^{-14} cm^3/mol-sec (20–30 °C) (Butler et al. 1978; Chang and Kaufman 1977; Cox et al. 1976; Crutzen et al. 1978; Howard and Evenson 1976; Jeong et al. 1984). More recent work indicates that this rate constant ranges from 0.95×10^{-14} cm^3/mol-sec to 1.2×10^{-14} cm^3/mol-sec (Finlayson-Pitts et al. 1992; Jiang et al. 1992; Lancar et al. 1993; Talukdar et al. 1992). 1,1,1-Trichloroethane is degraded via H-atom abstraction to $CCl_3\dot{C}H_2$ and reacts with O_2 to yield the peroxy radical ($CCl_3CH_2\dot{O}_2$) (DeMore 1992; Spence and Hanst 1978). Using an estimated atmospheric hydroxyl radical concentration of 5.0×10^5 mol/cm^3 (Atkinson 1985), the more recent rate constants translate to a calculated lifetime or residence time of ≈6 years. The estimated atmospheric lifetime of 1,1,1-trichloroethane which incorporates all removal processes, was also estimated to be ≈6 years (Prinn et al. 1987; Prinn et al. 1992). This indicates that the predominant tropospheric sink of 1,1,1-trichloroethane is through its reaction with OH radicals.

Photolytic degradation experiments have been performed in the presence of NO and NO_2; 1,1,1-trichloroethane underwent <5% degradation in 24 hours in the presence of NO (Dilling et al. 1976). In a smog chamber experiment in the presence of NO_x, 1,1,1-trichloroethane showed a disappearance rate of 0.1% per hour (Dimitriades and Joshi 1977). Other studies have also concluded that 1,1,1-trichloroethane has low potential to form ozone as a result of photochemical reaction in the presence of NO_x (Andersson-Skoeld et al. 1992; Derwent and Jenkin 1991).

Under laboratory conditions thought to mimic atmospheric smog conditions, direct photochemical irradiation of 1,1,1-trichloroethane in the presence of elemental chlorine was performed. 1,1,1-Trichloroethane was the least reactive and thus the most stable of all chloroethanes under these conditions (Spence and Hanst 1978).

Direct photochemical degradation of 1,1,1-trichloroethane in the troposphere is not expected to be an important fate process, because there is no chromophore for absorption of ultraviolet light (>290 nm) found in sunlight at tropospheric altitudes (Hubrich and Stuhl 1980; VanLaethem-Meuree et al. 1979). A laboratory experiment performed in sealed Pyrex ampules showed loss of 1,1,1-trichloroethane in

2 weeks under the influence of sunlight; however, catalysis by the Pyrex surface was probably responsible for the enhanced reactivity (Buchardt and Manscher 1978).

The relatively long tropospheric residence time for 1,1,1-trichloroethane suggests that migration to the stratosphere should be important. An estimated 11–15% of 1,1,1-trichloroethane released to the atmosphere is expected to survive and migrate to the stratosphere (Prinn et al. 1987; Singh et al. 1992). In the stratosphere, chlorine atoms produced from 1,1,1-trichloroethane by ultraviolet light may interact with ozone contributing to the destruction of the stratospheric ozone layer. Compared to CFC-11 (trichlorofluoromethane), the steady state ozone depletion potential of 1,1,1-trichloroethane has been estimated to be 0.1–0.16 (Gibbs et al. 1992; Solomon and Albritton 1992).

6.3.2.2 Water

Slow biodegradation of 1,1,1-trichloroethane can occur under both anaerobic and aerobic conditions. Anaerobic degradation of 1,1,1-trichloroethane is thought to occur predominantly through reductive dechlorination by methane-producing bacteria (Vargas and Ahlert 1987; Vogel and McCarty 1987) and by sulfate-reducing organisms (Cobb and Bouwer 1991; Klecka 1990). Determined experimental half-lives for anaerobic degradation using mixed culture bacteria ranged from 1 day to 16 weeks in the laboratory (Bouwer and McCarty 1983a, 1984; Hallen et al. 1986; Parsons et al. 1985; Vogel and McCarty 1987; Wood et al. 1985); based on a study from an injection well, after 3 months of injection, the predicted half-life of 1,1,1-trichloroethane in an aquifer was 200–300 days (Bouwer and McCarty 1984). Results obtained in a grab sample study of an aquifer suggest that anaerobic biodegradation of 1,1,1-trichloroethane will not occur (Wilson et al. 1983); however, the spiked concentration of 1,1,1-trichloroethane in the study, 1 mg/L, was in a range determined to be toxic to microorganisms (Barth and Bunch 1979; Benson and Hunter 1977; Vargas and Ahlert 1987). Another grab sample study, performed using more realistic concentrations, indicates that 1,1,1-trichloroethane slowly degrades under anaerobic conditions to 1,1-dichloroethane in groundwater (Parsons and Lage 1985; Parsons et al. 1985). However, when mixed anaerobic cultures were provided with acetate as primary substrate, the biodegradation of secondary substrate 1,1,1-trichloroethane occurred even without acclimation at concentrations exceeding 1 mg/L (Hughes and Parkin 1992). A laboratory study showed that anaerobic biodegradation of 1,1,1-trichloroethane did not occur under denitrification conditions even after 8 weeks of incubation (Bouwer and McCarty 1983b).

7 (Yao and Haag 1991). Therefore, reaction with ozone will not be an important process for the transformation of 1,1,1-trichloroethane present in natural bodies of water.

6.3.2.3 Sediment and Soil

Data are lacking on the degradation of 1,1,1-trichloroethane in soil. In a grab sample experiment, anaerobic degradation of 1,1,1-trichloroethane occurred slowly in soil (16% in 6 days) (Henson et al. 1988). If the microorganisms in the soil were first activated by using methane as a nutrient source, 46% of 1,1,1-trichloroethane degraded during the same period under aerobic conditions (Henson et al. 1988). Incubation of 1,1,1-trichloroethane in soil under aerobic conditions resulted in no measurable biodegradation (Klecka 1990).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

The manufacture and use of 1,1,1-trichloroethane was scheduled to be phased out by 2002 under the Clean Air Act (EPA 2004m). Since it is no longer in use, the levels estimated in the environment, other than near point sources, should drop to insignificant amounts.

6.4.1 Air

1,1,1-Trichloroethane has been identified in urban, rural, and indoor air throughout the United States at concentrations shown in Table 6-3. Due to the nature of 1,1,1-trichloroethane's use, volatilization to the atmosphere is a predictable outcome, and thus, its widespread detection is not unexpected. It is the only chlorinated ethane regularly seen as a background pollutant in the troposphere (Spence and Hanst 1978). For the year 1980, an estimated global atmospheric quantity of 1,1,1-trichloroethane, based on absolute concentrations obtained over a 3-year period, was 2.58×10^9 kg (5,690 million pounds) (Prinn et al. 1983). An estimated average concentration of 0.14 ppb in 1980, based on a characterization of its sources, abundance, and atmospheric sinks, was also reported (Ramanathan et al. 1985). The data indicate that the average atmospheric concentration of 1,1,1-trichloroethane was 0.13 ppb for the middle of 1988 (Khalil and Rasmussen 1989). Based on absolute concentrations obtained over a 12-year period, a global atmospheric concentration of 157 ppt (0.157 ppb) was estimated for 1,1,1-trichloroethane in the middle of

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1990 (Prinn et al. 1992). Atmospheric measurements at several surface stations made between 1978 and 1990 indicated that the global average concentration of 1,1,1-trichloroethane increased at a rate of 4.4±0.2% over this time period (Prinn et al. 1992).

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The measured concentration of 1,1,1-trichloroethane in urban air usually ranges from 0.1 to 1 ppb; however, levels ≤1,000 ppb have been observed in large urban areas or near hazardous waste sites. Representative monitoring data on the concentration of 1,1,1-trichloroethane in air can be found in Table 6-3. Rural levels of 1,1,1-trichloroethane are typically <0.2 ppb. The long atmospheric lifetime of 1,1,1-trichloroethane allows the compound to be carried a considerable distance from its initial point of release; detectable levels have been measured in numerous remote areas throughout the world and are shown in Table 6-3 (Class and Ballschmiter 1986; DeBortoli et al. 1986; Guicherit and Schulting 1985; Hov et al. 1984; Ohta et al. 1976; Rasmussen et al. 1982). The mean background concentration of 1,1,1-trichloroethane over subarctic North America in the summer of 1990 was 0.155 ppb (Wofsy et al. 1994). During a period of arctic haze, the concentration of 1,1,1-trichloroethane in the polluted Arctic air was 2–15% higher than in clean air over the Arctic (Khalil and Rasmussen 1993). The mean concentration of 1,1,1-trichloroethane in the troposphere over northwestern Pacific region (114–165 °E longitude) was found to range from 0.12 to 0.13 ppb (Blake et al. 1997, Table 6-3 Mohamed et al. 2002). The concentrations of 1,1,1-trichloroethane near industrial facilities emitting 1,1,1-trichloroethane were found to be only marginally higher than those measured at sites away from facilities emitting 1,1,1-trichloroethane.

The concentration of 1,1,1-trichloroethane in indoor air is variable, and seems to depend on individual practices, season, outdoor concentration, age of building, and building air-exchange characteristics (Cohen et al. 1989; Hartwell et al. 1987a, 1987b, 1992; Hisham and Grosjean 1991; Lioy et al. 1991; Wallace 1986; Wallace et al. 1986a, 1986b, 1988, 1989, 1991). For example, college students monitored simultaneously on the same campus were found to have levels of personal exposure varying by as much as two orders of magnitude (Wallace et al. 1982; Zweidinger et al. 1983). Further, two studies suggest that buildings with air conditioning may have higher levels of 1,1,1-trichloroethane in indoor air (Cohen et al. 1989; Hisham and Grosjean 1991). 1,1,1-Trichloroethane has been found at levels ≤70 ppb in newly constructed buildings (Wallace et al. 1987b). The concentration of 1,1,1-trichloroethane in new and recently renovated buildings was as high as 290 ppb (Rothweiler et al. 1992). New carpet and other new building materials that contain 1,1,1-trichloroethane may be responsible for higher levels in new and renovated buildings. During normal periods (no renovation or construction), the levels of total volatile

organics are inversely proportional to the air exchange rate of the building (Shields and Weschler 1992). Higher levels of 1,1,1-trichloroethane are expected to be found in indoor air during winter than any other season (Wallace et al. 1991). The effect of outdoor air on indoor air was demonstrated by the detection of higher levels of 1,1,1-trichloroethane during outdoor stagnation conditions when the levels were higher compared to levels under non-stagnation conditions (Lioy et al. 1991). Representative data taken from five geographic areas located throughout the United States report indoor concentrations of 0.3–4.4 ppb and outdoor concentrations of 0.11–0.92 ppb (Pellizzari et al. 1986). Several studies have determined the presence of 1,1,1-trichloroethane in products expected to be in most households (Section 6.5) (EPA 1987; Maklan et al. 1987; Sack et al. 1992; Spicer et al. 1987). An EPA Region V (Minnersota, Wisconsin, Michigan, Illinois, Indiana, and Ohio) National Human Exposure Assessment Survey (NHEXAS) detected a mean concentration of 1,1,1-trichloroethane to be 1.15 ppb in indoor air samples collected from residential areas from July 1995 to May 1997 (Bonanno et al. 2001). The maximum concentration of trichloroethane detected in the same study was 34 ppb. 2

6.4.2 Water

1,1,1-Trichloroethane has been identified in surface water, groundwater, drinking water, effluent, rain, snow, and urban runoff. The amount of the chemical detected in surface and groundwater depends upon the location of the sampling point. Concentrations in surface water removed from point-source emissions such as industrial waste water, hazardous waste sites, and spill locations are usually <1 ppb. In random samples of groundwater taken in the United States, concentrations have ranged from 0 to 18 ppb. Groundwater samples obtained near sources of release to soil or the ground have been as high as 11,000 ppb. Drinking water from surface or groundwater sources contained 1,1,1-trichloroethane concentrations of 0.01–3.5 ppb.

Data on the occurrence of 1,1,1-trichloroethane in water are presented in Table 6-2. Data on the concentration of 1,1,1-trichloroethane in effluent can be found in Table 6-4. not found in the package

1,1,1-Trichloroethane was found in groundwater at hazardous waste sites in 18.9% of 178 sites from the Comprehensive Emergency Response, Compensation and Liability Act (CERCLA) database, making it the seventh most frequently detected compound in this study (Plumb 1987). It was found in water

samples from 42 of 357 Contract Laboratory Program (CLP) sites; the concentration range of the mean values was 1.75–1,100 ppb (Viar 1987).

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6.4.3 Sediment and Soil

Monitoring data on the occurrence of 1,1,1-trichloroethane in soil are not as extensive as for water or air, which precludes an estimate of typical levels found in soil. The reported levels of 1,1,1-trichloroethane in soils are shown in Table 6-5. In two grab soil samples taken in 1980 from two former sludge lagoons of a solvent recovery operation at Southington, Connecticut, the measured concentrations of 1,1,1-trichloroethane were 23,000 and 120,000 ppb (Hall 1984). The limited data on the concentration of 1,1,1-trichloroethane in soil may be due to its rapid volatilization from soil, its ability to leach through soil, or both. The concentrations of 1,1,1-trichloroethane in sediments are shown in Table 6-2. The mean concentration of 1,1,1-trichloroethane in sediments from a river passing through an industrial area in Japan was 0.4 ppb, although it was not detected in the river water or in the sediment of a river passing through a non-industrial area (Grotoh et al. 1992).

6.4.4 Other Environmental Media

Limited data on the occurrence of 1,1,1-trichloroethane in other media were located. 1,1,1-Trichloroethane has been found in raw, processed, and prepared food products. These data are presented in Table 6-6. 1,1,1-Trichloroethane has been found in fish and shrimp taken from the Pacific Ocean at average concentrations of 2.7 and <0.3 ppm, respectively (Young et al. 1983). It has also been detected in clams and oysters from Lake Pontchartrain, Louisiana, with mean concentrations ranging from 39 to 310 ppm (Ferrario et al. 1985) and from a polluted river in Japan at concentrations ranging from 0.6 to 1.8 ppb wet weight (wt/wt) (Grotoh et al. 1992). 1,1,1-Trichloroethane was detected in 2 of 265 table-ready foods of FDA Total Diet Study at an average concentration of 12.7 ppb (Heikes et al. 1995).

1,1,1-Trichloroethane has been detected in four shoe and leather glues in Denmark in the concentration range 0.1–2.7% (wt/wt) (Rastogi 1992). Six samples of glues manufactured in the United States and in Europe and used for assembling various consumer goods and toys contained 1,1,1-trichloroethane in the concentration range 0.002–97.5% (wt/wt) (Rastogi 1993). In various brands of imported typing

correction fluids in Singapore, the equilibrium vapor phase concentration of 1,1,1-trichloroethane ranged from <1 to 95% (v/v) (Ong et al. 1993).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The manufacture and use of 1,1,1-trichloroethane was scheduled to be phased out by 2002 under the Clean Air Act (EPA 2004m). Since it is no longer in use, the exposure of the general population should drop to insignificant levels.

The ubiquitous occurrence, in the past, of low levels of 1,1,1-trichloroethane in ambient air and other environmental samples, together with the fact that many consumer products used to contain this chemical, suggests that much of the general population of the United States was exposed to low levels of 1,1,1-trichloroethane. This exposure could have occurred occupationally, environmentally, or as a result of the use of commercial products that contain 1,1,1-trichloroethane. 1,1,1-Trichloroethane has been detected in the blood, milk, breath, and urine of humans. An EPA Region V (Minnersota, Wisconsin, Michigan, Illinois, Indiana, and Ohio) National Human Exposure Assessment Survey (NHEXAS) detected a mean concentration of 1,1,1-trichloroethane to be 0.05 ppb in blood samples collected from July 1995 to May 1997 (Bonanno et al. 2001). The maximum concentration of trichloroethane detected in the same study was 2.7 ppb. Data on human body burdens associated with this compound can be found in Table 6-7. Table 5-2 provides a sampling of consumer products containing 1,1,1-trichloroethane. The levels of this chemical in human breath have been correlated with its levels in personal air by probability-based population studies (Wallace et al. 1985, 1986c, 1987a, 1988).

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Not in the package

If the average urban concentration of 1,1,1-trichloroethane is taken to be 1 ppb and the average rural concentration is taken to be 0.1 ppb, then daily non-occupational intakes of 108 and 10.8 μg/day, respectively, can be obtained based on an average human air intake of 20 m^3/day. In areas where 1,000 ppb have been measured, the daily intake using this methodology would be 108 mg. However, Wallace et al. (1984a) have determined that the mean daily air exposure for 12 subjects from urban New Jersey and Research Triangle Park, North Carolina, was 370 mg. Further, the mean daily intake from all sources (air, food, and water) was between 50 and 1,000 mg/day for 1,1,1-trichloroethane (Wallace et al. 1984a).

1,1,1-Trichloroethane has been detected in newly constructed buildings (Wallace et al. 1987b). In a recent "shopping basket" survey, 1,1,1-trichloroethane was found in 216 of 1,159 common household products preselected to contain solvents at concentrations >0.1% by weight (Sack et al. 1992). In a similar study, 1,1,1-trichloroethane was found in all 67 categories of household products (1,026 brands tested) likely to be in the average U.S. home (EPA 1987; Maklan et al. 1987). The categories of these common household products are given in Table 5-2. The occurrence of 1,1,1-trichloroethane in 62% of the effluent samples taken from a community septic tank also suggests the presence of this compound in household products (De Walle et al. 1985). not in the package

Human exposure could occur directly via ingestion of contaminated water, but also indirectly through the inhalation of 1,1,1-trichloroethane that has volatilized from contaminated tap water. Based on a theoretical concentration of 1 mg/L (ppm) of 1,1,1-trichloroethane in tap water, the average estimated air concentrations for the entire house, bathroom, and shower stall were 2.3×10^{-4}, 5.1×10^{-3}, and 2.6×10^{-2} mg/L, respectively (McKone 1987). For a tap water concentration of 20 mg/L, the estimated daily exposure to 1,1,1-trichloroethane was 20.0 mg from ingestion and 22.8 mg from inhalation while showering (Foster and Chrostowski 1986). The Total Exposure Assessment Methodology (TEAM) studies demonstrated that levels of personal air exposure determined using samples obtained on the same day could vary by orders of magnitude for subjects living in the same municipality, most likely as a result of variances in consumer practices and occupation (Hartwell et al. 1987a, 1987b, 1992; Wallace 1986, 1987; Wallace et al. 1986a, 1986b, 1988, 1989; Zweidinger et al. 1983). The maximum exposure levels of 1,1,1-trichloroethane during personal activities were: 185 ppb when visiting the dry cleaners, 18.5 ppb when working in a chemistry lab, 12 ppb when working as a lab technician, 48 ppb when using household cleaners, 20 ppb when using pesticides, and 20 ppb when using paint (Wallace et al. 1989). Exposure of the general population from the use of commercial products may be more significant than exposure resulting from industrial release.

According to the National Occupational Exposure Survey (NOES) conducted by NIOSH between 1981 and 1983, it has been statistically estimated that ≈2,528,300 workers in the United States were potentially exposed to 1,1,1-trichloroethane (NIOSH 1990). The largest number of workers are exposed in the following types of industries/services: sewing machine operators in apparel industry; registered nurses, maids, janitors and cleaners in hospitals; electricians, technicians, assemblers, installers, machinists and repairers in electrical and electronic industry; and janitors and cleaners in building maintenance service. From the existing monitoring data, it appears that most occupational exposure occurs by inhalation.

Specific industrial applications of 1,1,1-trichloroethane that might result in elevated levels of exposure are processes involving the degreasing and cleaning of fabricated metal parts (Gunter et al. 1977; Kominsky 1976; Levy and Meyer 1977; Markel 1977), manufacture of electronic components (Giles and Philbin 1976), mixing and application of commercial resins (Giles 1976), and spray painting and spray gluing (Whitehead et al. 1984). Table 6-8 lists occupations in which 1,1,1-trichloroethane has been detected in the air. Other occupations where workers can be exposed to 1,1,1-trichloroethane include automotive assembly plants (Nelson et al. 1993), kraft pulp mills (Rosenberg et al. 1991), and fuel cell assembly plants (NIOSH 1993). In a survey (1990–1991) of a fuel cell assembly plant, the levels of 1,1,1-trichloroethane in some of the personal breathing zone and general area samples were found to exceed the NIOSH short-term exposure limit of 350 ppm (NIOSH 1993).

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6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

The manufacture and use of 1,1,1-trichloroethane was scheduled to be phased out by 2002 under the Clean Air Act (EPA 2004m). Since it is no longer in use, exposure of children should drop to insignificant levels.

Exposures of the embryo or fetus to volatile organic compounds such as 1,1,1-trichloroethane may occur if the expectant mother is exposed. A newborn infant may be exposed by breathing contaminated air and through ingestion of mother's milk that can contain small amounts of 1,1,1-trichloroethane. Children may be exposed through accidental ingestion of products containing 1,1,1-trichloroethane. Older children and adolescents may be exposed to 1,1,1-trichloroethane in their jobs or hobbies, or through deliberate solvent abuse by "sniffing." Epidemiological studies and case reports discussing reproductive and/or developmental toxicity of 1,1,1-trichloroethane in humans have been reviewed in Chapter 3.

Young children often play close to the ground and frequently play in dirt, which increases their dermal exposure to toxicants in dust and soil. They also tend to ingest soil, either intentionally through pica or unintentionally through hand-to-mouth activity. Children, thus, may be orally and dermally exposed to 1,1,1-trichloroethane present as a contaminant in soil and dust. 1,1,1-Trichloroethane has a log organic carbon-water partition coefficient of 2.03, indicating low adsorption to soil (Chiou et al. 1979; Friesel et al. 1984). Most of the 1,1,1-trichloroethane present in the upper layers of the soil is volatilized to air within 24 hours (vapor pressure =124 mm Hg at 25 °C, Boublik et al. 1984). The rapid volatilization of 1,1,1-trichloroethane results in inhalation being the most likely route of exposure.

Children breathe in more air per kilogram of body weight than an adult. Therefore, a child in the same micro-environment as an adult is likely to be exposed to more 1,1,1-trichloroethane from ambient air. Young children are closer to the ground or floor because of their height. The 1,1,1-trichloroethane vapors being heavier than air (vapor density =4.63 g/mL; HSDB 2004) tend to concentrate near the ground. The children, therefore, are at a greater risk of exposure than adults during accidental spills of 1,1,1-trichloro-ethane.

Children may also be exposed to fumes of 1,1,1-trichloroethane by working with or playing near sources. Children's exposure also occurs through accidental ingestion and inhalation of the chemicals into the lungs. Children are also exposed to higher concentrations of 1,1,1-trichloroethane (0.1–1 ppb, Table 6-3) in urban areas compared to children living in rural areas (concentrations typically <0.2 ppb, Table 6-3). not in the package

Animal studies demonstrated that, once absorbed, 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, including developing fetuses, with preferential distribution to fatty tissues (Holmberg et al. 1977; Katagiri et al. 1997; Schumann et al. 1982a; Takahara 1986b).

There are no existing studies that have monitored the level of exposure from 1,1,1-trichloroethane to children. Most uses of 1,1,1-trichloroethane are associated with occupational purposes, so it is unlikely that children will receive significant doses. Under extreme conditions where products containing high concentrations of 1,1,1-trichloroethane are used in the presence of children in an enclosed area with little or no ventilation, children could receive significant exposure. There are studies that examine the exposure to children from parents' work clothes, skin, hair, tools, or other objects removed from the workplace (NIOSH 1995); however, this type of "take home" or secondary exposure is unlikely due to the high volatility of methylene chloride. Additional exposure from consumer products can occur, but is unlikely to be significant, although little data are available at this time. ?

It is not known whether children differ in their weight-adjusted intake of 1,1,1-trichloroethane. However, children drink more fluids per kg of body weight than adults (NRC 1993) and 1,1,1-trichloroethane has been detected in drinking water (Section 6.4.2, Table 6-2).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

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The general population is potentially exposed to low levels of 1,1,1-trichloroethane through the ingestion of contaminated water or food. The manufacture and use of 1,1,1-trichloroethane was scheduled to be phased out by 2002 under the Clean Air Act (EPA 2004m). Since it is no longer in use, the exposure of the general population should drop to insignificant levels. Low levels of contamination in drinking water sources have been documented (Althoff et al. 1981; Barkley et al. 1980; Burmaster 1982; EPA 1986a; Krill and Sonzogni 1986; Wallace et al. 1984a; Zaki 1986). According to Table 6-2, levels of 0.01–12,220 ppb 1,1,1-trichloroethane have been found in drinking water sources. 1,1,1-Trichloroethane is used as a component of adhesives for food packaging, and this practice may contribute to human exposure by ingestion (Miller and Uhler 1988). Airtight, highly-insulated houses are likely to have high indoor concentrations from use of household products containing 1,1,1-trichloroethane. Very high levels of exposure are expected to occur for those who intentionally inhale 1,1,1-trichloroethane for its euphoric/narcotic properties.

Workers involved in processes using this compound may encounter high exposure levels. Occupations in which 1,1,1-trichloroethane has been found in the air are given in Table 6-8. Analysis of these data

volume of 1,1,1-trichloroethane produced in the United States is known. According to the 1990 amendments to the Clean Air Act and the Montreal Protocol, future U.S. production will be cut incrementally until phase-out by January 1, 2002 (EPA 2004m). The large annual production of this compound and its presence in consumer products indicate that a large segment of the general population could potentially be exposed to 1,1,1-trichloroethane. The use of 1,1,1-trichloroethane is well-documented. It was used extensively in industrial applications, and it was found in numerous consumer products for the home. Mandates on production, however, are expected to decrease the use of 1,1,1-trichloroethane and subsequent potential exposure to 1,1,1-trichloroethane.

There are a few food monitoring studies in the literature that provide several examples of food contamination with 1,1,1-trichloroethane. The ubiquitous nature of 1,1,1-trichloroethane suggests that additional information in this area would allow a complete determination of the levels of human exposure to this chlorinated solvent. The release of 1,1,1-trichloroethane to the environment is well established since there are numerous studies that indicate the presence of this compound in environmental media. The quantity of 1,1,1-trichloroethane released to the environment during its production, formulation, and use is known. 1,1,1-Trichloroethane is listed on the Toxics Release Inventory (TRI). Methods for the disposal of 1,1,1-trichloroethane exist. Data on the removal of 1,1,1-trichloroethane from waste streams during biological treatment processes are lacking. Information on the amount of 1,1,1-trichloroethane disposed of annually is scarce. Rules and regulations governing the disposal of 1,1,1-trichloroethane exist.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. ~~The Toxics Release Inventory (~~TRI~~)~~, which contains this information for 2001, became available in 2002. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Data on the environmental fate of 1,1,1-trichloroethane are well represented in the literature. The partitioning of 1,1,1-trichloroethane from soil or water to the atmosphere is well established, and there is sufficient evidence to indicate that the compound can leach into groundwater. The relatively slow rate of degradation and the major routes of 1,1,1-trichloroethane degradation in all environmental compartments have been established. The relatively long persistence of 1,1,1-trichloroethane in the atmosphere indicates that a significant portion of this compound migrates to the stratosphere. Data on the biodegradation of 1,1,1-trichloroethane in soil are particularly lacking.

Researchers at Physical Optics Corporation (POC) proposes to develop a group-specific active optical chemical sensor for halohydrocarbons (including trichloroethylene, dichloroethylene, perchloroethylene, and 1,1,1-trichloroethane) that can be interfaced with a cone penetrometer for subsurface applications. No liquid chemical substances will be used in the final sensor design, enabling simple fiber optic-based downhole deployment.

Researchers at University of Washington, College of Forest Resources propose to test the ability of several plant strains to take up and transform various chlorinated hydrocarbons, including carbontetrachloride, chloroform, bischloromethane, 1,1,1-trichloroethane, perchloroethylene, trichloroethylene, dichloromethanes, and vinyl chloride using laboratory mass balance reactors. They will identify the mechanisms involved in the chlorinated hydrocarbon oxidation in poplar and use molecular methods to enhance that activity.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring 1,1,1-trichloroethane, its metabolites, and other biomarkers of exposure and effect to 1,1,1-trichloroethane. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

In the analysis of 1,1,1-trichloroethane in biological materials, a key factor in the determination is the sample matrix under consideration. In the broadest sense, this can be broken down into liquid samples (e.g., blood or urine), solid samples (which would include adipose tissue, liver samples), and expired air samples. After 1,1,1-trichloroethane has been liberated from the sample matrix, a number of similar techniques can then be used to complete the analysis. A synopsis of these methods can be found in Table 7-1. In general, the methods for determining the metabolites of 1,1,1-trichloroethane are the same as those used for the parent compound, with slight modifications (Nolan et al. 1984). not in the Package

The quantification of 1,1,1-trichloroethane in blood and urine samples can be achieved by the initial use of purge and trap methodology (Antoine et al. 1986; Barkley et al. 1980). This technique involves the liberation of the volatile chlorinated hydrocarbon by bubbling an inert gas through the sample matrices at elevated temperatures (≈50–95 °C). Higher temperature increases the vapor pressure of the compound, and the bubbling action serves, essentially, to increase the gas-liquid partition, and thus volatilize the compound of interest. The gaseous sample is collected on an adsorption tube, which frequently uses a polymeric sorbent such as Tenax GC.

At this point, the sample is analyzed by gas chromatography (GC), the analytical method of choice for volatile halogenated hydrocarbons. Information on the analysis of these samples by GC is presented in Section 7.2, with a discussion of the advantages and disadvantages of each method. The technique of Antoine et al. (1986) showed a 5% variance on a series of 2 ppb spiked samples, and the analysis had a linear response ranging from 0.5 to 50 ppb. Although infra-red spectrometry has less sensitivity than electron capture detectors (ECD), Hall electroconductivity detectors (HECD), and mass spectrometric detectors (MS), it has been used to quantify the levels of 1,1,1-trichloroethane in biological samples (IARC 1979).

The concentration of 1,1,1-trichloroethane in solid samples can be determined by headspace techniques, which involve analysis of the air above a heated sample in either a dynamic or a static system. In a static system, an aliquot of the atmosphere above the sample is obtained and analyzed by direct GC. In a dynamic system, an inert gas is passed over the top of a heated, rapidly stirred suspension of sample in water (Stanley 1986a, 1986b). The gas stream is then passed through an adsorption tube, trapping the volatile compounds. For adipose tissue, the detection limits were 0.01 mg/kg and the average recovery for spiked samples (concentration range 0.15–0.44 μg/20 g tissue) was 105%, with a precision of 11.8% (Stanley 1986a, 1986b).

In biological samples, losses during the sample preparation stage (weighing, transferring, etc.) can arise due to the volatility of 1,1,1-trichloroethane or from an incomplete recovery from the biological matrix. Samples should be analyzed shortly after they are obtained. Otherwise, they should be carefully stored at low temperature, preferably in a freezer. Handling and manipulation also should be kept to a minimum, preventing both premature loss by volatilization and contamination of the sample through the adsorption of vapors from ambient air. The need for blank water with very low levels of volatile organic compounds (VOCs) has increased because of the constant improvement in the sensitivity of detection of these VOCs. A method that uses distillation in conjunction with helium stripping has been described to obtain high purity blank water (Cardinali et al. 1994).

7.2 ENVIRONMENTAL SAMPLES

A short description of the methods used for analysis of 1,1,1-trichloroethane in environmental samples is presented in Table 7-2. An extensive list of methods for analysis of 1,1,1-trichloroethane in not in the package

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methodology for determining the levels of 1,1,1-trichloroethane and its biotic/abiotic degradation products such as 1,1-dichloroethene, 1,1-dichloroethane, and chloroethane in environmental samples are well established (Hallen et al. 1986; Mehran et al. 1988a; Parsons et al. 1985; Vogel and McCarty 1987). Existing methods that provide acceptable detection limits for background levels in the environment and for levels at which health effects occur can be found for all types of environmental samples. The precision, accuracy, reliability, and specificity of each method are well documented, and potential pitfalls have been described. Development of a new methodology to determine 1,1,1-trichloroethane in environmental samples that would provide both increased speed and decreased levels of difficulty may be desirable in situations where environmental monitoring of 1,1,1-trichloroethane is required on a rapid or routine basis.

position of chlorine is not defined

7.3.2 Ongoing Studies

No ongoing studies involving analytical techniques of 1,1,1-trichloroethane were found in a search of the Federal Research in Progress database (FEDRIP 2004).

8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding 1,1,1-trichloroethane in air, water, and other media are summarized in Table 8-1. Not found in the package

ATSDR has derived an MRL of 20 mg/kg/day for acute-duration inhalation exposure (14 days or less) to 1,1,1-trichloroethane, based on a LOAEL of 175 ppm for reduced performance of psychomotor tests in human volunteers in a study by Mackay et al. (1987).

ATSDR has derived an MRL of 0.7 ppm for intermediate-duration inhalation exposure to 1,1,1-trichloroethane based on a study by Rosengren et al. (1985), which found evidence of astrogliosis (increased glial fibrillary acid protein levels) in the brains of gerbils exposed to 210 or 1,000 ppm, but not 70 ppm, of 1,1,1-trichloroethane continuously for 3 months.

ATSDR has derived an MRL of 20 ppm for intermediate-duration oral exposure to 1,1,1-trichloroethane based on a NOAEL of 1,770 mg/kg/day for body weight effects in male mice administered 1,1,1-trichloroethane in the daily diet for 13 weeks (NTP 2000).

The EPA does not list a reference concentration or a reference dose for 1,1,1-trichloroethane on the Integrated Risk Information System (IRIS 2004). The EPA has classified 1,1,1-trichloroethane as group D, not classifiable as to human carcinogenicity, based on no reported human data and inadequate animal data (IRIS 2004).

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Table 3-1 Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Wistar)	Once 6-420 min				14250 (LC50 - 7 hr)	Adams et al. 1950
2	Rat (Sprague-Dawley)	1 d 6 hr/d				10305 M (LC50 - 6 hr)	Bonnet et al. 1980
3	Rat (Alderley Park)	1 d 10-15 min/d				38000 (LC50 - 15 min)	Clark and Tinston 1982
4	Mouse (OF1)	1 d 6 hr/d				13414 F (LC50 - 6 hr)	Gradiski et al. 1978
5	Mouse (NA2)	1 d 2 hr/d				3911 M (LC50 - 2 hr)	Horiguchi and Horiuchi 1971
6	Mouse (CD-1)	1 d 10-60 min/d				18358 M (LC50 - 60 min)	Moser and Balster 1985
7	Mouse (CD-1)	1 d 30 min/d				22241 M (LC50 - 30 min)	Woolverton and Balster 1981

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
Death								
452 Human 29B	NS	NS	CS					Bass 1970
where this is marked in bibliography?								
Comments: This is a survey of "sudden sniffing death" cases during the 1960's. Of 110 cases identified, 29 were attributed to inhalation of 1,1,1-TCE.								
487 Human 1F	once	NS	OW GN HP CS					Caplan et al. 1976
Comments: This is a case report of a 40 year old woman who was exposed by inhalation to 1,1,1-TCE while refinishing a room without ventilation and with the door closed. The air concentration was not estimated. The woman died, and although the cause of death was not reported, pulmonary congestion and edema were observed upon histopathologic examination.								
453 Human 1M	NS	NS	GN CS					D'Costa and Gunasekera 1990
Comments: Case report of a 15-year old boy who died after intentionally inhaling typewriter correction fluid containing 1,1,1-TCE. Patient complained of double vision and hallucinations prior to death. Autopsy revealed a grossly edematous brain, as well as edema in the lungs, liver and gut. The heart was normal. Blood concentration of 1,1,1-TCE was 1.7 mg/L, 1,1,1-TCE was also detected in the brain and liver.								
507 Human 2M	<45 min	NS	CS OR					Droz et al. 1982
Comments: This is a report of 2 cases chosen to illustrate sudden death in men following intentional inhalation of 1,1,1-TCE. Simulations of the fatal air concentrations showed exposure levels between 6,000 and 20,000 ppm. Both men died following reanimation attempts. One of the men showed ventricular fibrillation, but no other signs of life. The other man was diagnosed with cerebral death. Howevere, no anatomical cause of death was found at autopsy in either case.								
470 Human 1M	once	NS	OW GN HP CS					Gresham and Treip 1983
:nts: This is a case report of an 18 year old man who entered a coma after being discovered with his head in a puddle of 1,1,1-TCE. The coma had lasted for at least 3 years before the man died. The air concentration during exposure was not estimated. The man died of bronchopneumonia after a 39 month coma.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
534 Human 1M	once	NS	GN HP CS OR					Guberan et al. 1976
Comments: Case report of a 20 year old man who intentionally inhaled 1,1,1-TCE. Vomiting was followed by ventricular fibrillation and death. No lesions were found in the heart at autopsy.								
514 Human 1M,1F	once	NS	OW GN HP CS					Hall and Hine 1966
Comments: This is a report of 2 cases, one a 29 year old man and the other a 19 year old woman, who apparently inhaled a lethal concentration of 1,1,1-TCE. The fatal concentrations were not estimated, although the woman had been sniffing cleaning fluid for several days, and the man had died with a rag soaked in cleaning fluid over his mouth. Both people died of unspecified causes. In the man, the weight of both lungs was markedly increased and edematous, the lungs and bronchi contained blood-tinged white frothy fluid, while the pulmonary parenchyma showed considerable congestion and edema with patchy hemorrhage. The kidney showed vascular congestion, and the blood contained 13.0 mg% 1,1,1-TCE. The woman's lungs were similar, with passive congestion throughout, and parenchyma with bloody, frothy fluid. Microscopic examination revealed edema, and congestion of the pulmonary parenchyma with atelectasis in the woman. The woman's brain showed acute passive congestion.								
496 Human 1M	<1 hr	NS	GN CS					Jones and Winter 1983
Comments: This is a case report of a 17 year old man who was found unconscious after less than 1 hour of accidental inhalation exposure. The man had been cleaning the upholstery of a car, with one door of the car open for ventilation. A simulation of the circumstances of his death revealed a possible exposure concentrations of 6410 ppm at the location of the man's face upon discovery, although the authors note that anesthesia by inhalation of 1,1,1-TCE probably requires an air concentration of 10,000 to 26,000 ppm. The man was taken by ambulance to a hospital, and was discovered to be dead on arrival. Post-mortem revealed his bronchi to be blocked with vomitus. After less than 1 hour of exposure the man apparently died of asphyxiation after vomiting as a result of intoxication by 1,1,1-TCE.								
499 Human 1M	<2 hr	NS	GN BC CS					Jones and Winter 1983
Comments: This is a case report of a 20 year old man who died after less than 2 hours of inhalation exposure and probable concurrent dermal expsoure to 1,1,1-TCE while using the solvent as a degreasing agent. The concentration in the room was apparently not measured, although the room was noted to be "fume-filled," and solvent-induced dermal changes were observed on all exposed skin. After an inquest, death was reported to have been caused by respiratory suppression that was secondary to central nervous system depression.								

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Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Inhalation

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
512 Human 2M,2F	NS	NS	GN HP CS					King et al. 1985
Comments: This is a report of 4 cases of young adults (aged 13-18 years old) who intentionally sniffed TCF (liquid paper), which contains 1,1,1-TCE. The air concentration of the solvent was not estimated. TCF also contains trichloroethylene, among other constituents. All 4 youths died. All of the adolescents collapsed suddenly within several hours of sniffing the TCF. Three showed either pulmonary blockage, fluid, or hemorrhaging. Two had heart anomalies, and 1 showed evidence of subcutaneous drug use. Three of the subjects were physically exerting themselves when they collapsed. The circumstances of death suggest that they suffered from a fatal cardiac arrhythmia.								
517 Human 3M	once	NS	GN CS					MacDougall et al. 1987
Comments: This is a report of 3 fatal cases of inhalation of 1,1,1-TCE in a thinning fluid (Tipp-Ex) in boys of 13-15 years of age. The air concentrations of the solvent, and other solvents in the thinner were not reported. All 3 boys died suddenly, apparently during or immediately following inhalation of the thinner fumes. The cause of death was not reported, however pulmonary congestion and edema were reported, as well as hemorrhaging and frothy fluid in the lungs, and inhalation of aspirated gastric contents.								
493 Human 52B	NS	NS	CS					McCarthy and Jones 1983
Comments: This is a reveiw of 52 case reports of accidental and intentional human exposure to 1,1,1-TCE. The study examines case reports of several other chemicals, as well. The primary route of exposure was inhalation. The incidence of mortality among the case reports was 2/52.								
489 Human 1M	once	NS	CS					Northfield 1981
Comments: A young man of 15 years died on the job while degreasing small metal "parts" by running the solvent on the parts, over an open tank of 1,1,1-TCE. He was found slumped into the tank with his head touching the solvent. Subsequent investigation of the site of death revealed that when the solvent was not disturbed in the tank, air concentrations of 200, 6000, and >70,000 ppm were respectively recorded at 15 cm above the tank's rim, 8-15 cm below the tank's rim, and 8-15 cm above the surface of the solvent. When the solvent was disturbed, concentrations rose to 73,000 and 94,000 ppm at 8 cm above and 15 cm below the rim of the tank, respectively. The cause of death was reported to be cardiorespiratory failure.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
481 Human 1M	once	NS	GN HP CS					Stahl et al. 1969
Comments: This is a case report of a young man of 17 years who died while using 1,1,1-TCE in a small room, less than 7.75 hours after beginning the job. The air concentration of the solvent was not reported. At autopsy, the brain was moderately congested, with a lactic acid concentration of 226 mg/100 g, and a solvent concentration of 0.32 mg/100 g. Cyanosis of the skin was observed at autopsy. The liver, kidney, and spleen were moderately congested and the lung showed "marked" edema. There was also evidence that gastric contents were aspirated.								
484 Human 1M	once	NS	GN HP CS					Stahl et al. 1969
Comments: This is a case report of an obese 24 year old man who died after inhaling an unknown concentration of 1,1,1-TCE for less than 2 hours. An autopsy was conducted. The cause of death was not explicitly reported. At autopsy, cyanosis of the head and neck were observed. Congestion of the brain, spleen, kidneys, and lungs were reported, with edema in the lungs. Histological examination revealed centrilobular fatty change. The heart was 550 g, and moderate coronary atherosclerosis was observed. Congestion of the brain was noted at autopsy, and lactic acid concentration in the brain was reportedly 125 mg/100 g.								
776 Human 1M	NS (Occup)	NS						Sullivan 1994 1,1,1-trichloroethane
Descriptions: A male construction worker was found unconscious in a trench several hours after he had begun to apply a waterproofing sealant (containing 70% 1,1,1-trichloroethane) to a foundation wall. The worker succumbed shortly thereafter. Death was attributed to 1,1,1- trichloroethane intoxication.								
466 Human 1M	once	NS	OW GN HP BC CS OR HE					Travers 1974
Comments: This is a case report of an 18 year old man who apparently intentionally inhaled straight 1,1,1-TCE. The man was administered emergency care immediately upon collapsing, an unreported time after inhaling 1,1,1-TCE. The man died 24 hours after he collapsed, and an unknown time after inhaling 1,1,1-TCE. After 6 hours, the man was cyanotic, with no corneal reflex, absence of doll's eye signs, and aimless response to painful stimulus. ECG revealed ventricular tachycardia, and he showed gross hematuria. Hypotension and bradycardia were progressive and cardiac arrest repeated until his death. The right and left lungs were congested, and weighed 600 and 800 g, respectively. Atrial and ventricular dialation were evident, with some ventricular subendocardial hemorrhage. No detectable 1,1,1- TCE was evident in blood, brain, liver, and kidney tissues. WBC count was increased about 3 times over the normal level, serum potassium and chloride were decreased from normal, serum hemoglobin was slightly increased, and serum osmolarity and pH were elevated.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
412 Rat 5M,5F (Sprague-Dawley)	1 d 4 hr/d	13000, 14000, 16000	BW GN CS				14504 (LC50-4 hour)	Terrill 1989c
Comments: COMMENTS: Sprague-Dawley rats were exposed to vapor generated from aerosolized 1,1,1-TCE (96% pure containing 2.6% dimethoxymethane, 1% sec-butanol, and 0.4% 1,2-epoxybutane). The measured particulate level was <01% of vapor levels. There was a 14-day observation period. 95% CI on LC50: 13949-15590 ppm. Lethargy, respiratory distress and prostration was observed during exposure. All deaths occurred during exposure, and survivors generally appeared normal during the observation period. No effects on body weight were observed. Lesions in animals that died reflected postmortem changes. No treatment-related lesions occurred in survivors.								
410 Rat 5M,5F (Sprague-Dawley)	1 d 4 hr/d	13000, 14000, 16000	BW GN CS				14828 (LC50)	Terrill 1989d
Comments: Sprague-Dawley rats were exposed for a 14 day observation period to vapor generated from aerosolized 1,1,1-TCE (96.7% pure containing 1.2% t-butyl alcohol, 1.6% dimethoxymethane, and 0.5% 1,2-epoxybutane). The measured particulate level was <1% of vapor levels. 95% CI on LC50: 14082-15612 ppm. Lethargy, respiratory distress, prostration, and ataxia were exhibited during exposure. All deaths occurred during exposure, and survivors generally appeared normal during the observation period. No effect on body weight was observed. Necropsy of animals that died revealed dark or mottled lungs, dark nose turbinates, and enlarged spleens (all probably postmortem changes). No treatment-related lesions occurred in survivors.								
369 Mouse 5M,5F (B6C3F1)	1 d 6hr/d	0, 5000	BW GN					Calhoun et al. 1981
Comments: Male and female B6C3F1 mice received a single 6-hour inhalation exposure to 5000 ppm 1,1,1-TCE followed by a 2-day observation period. Mice were evaluated for clinical signs of toxicity and gross pathology. No mice died either during the exposure or during the 2-day observation period. No gross lesions observed.								

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Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Inhalation

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
142 Mouse NS (NS)	1 d 2hr/d	11900	CS				11900 (min lethal conc)	Lazarew 1929
Calculations: 65 mg/l x 1000 l/m3 x 24.45 x 1/133.41 = 11,900 ppm.								
Comments: Mice were placed in 10 l bottles containing 1,1,1-TCE vapor.								
242 Mouse LSE 12M (CD-1)	1 d 10-60 min/d	3000- 40000	CS				18358 M (LC50 - 60 min)	Moser and Balster 1985
Comments: CD-1 mice exposed to 1,1,1-TCE using static exposure. LC50 determined by Bliss probit method. Most deaths within 1 hr of end of exposure. LC50 decreased from 29,492 ppm after 10 minute exposure to 20,616 ppm after 30 minute exposure to 18,358 ppm after 60 minute exposure (95% CI: 17,726-19,012 ppm).								
211 Mouse LSE 12M (CD-1)	1 d 30 min/d	0, 3600- 23000	CS				22241 M (LC50 - 30 min)	Woolverton and Balster 1981
Comments: CD-1 mice exposed to 1,1,1-TCE inhibited with 3% dioxane. LD50 (calculated by Bliss probit method) after 30 minute exposure was 22,241 ppm (95% CI: 22,080-22,404).								
259 Dog 11NS (NS)	NS	NS (ml/kg)	CS				0.6 (death)	Krantz et al. 1959
Comments: Tested use of 1,1,1-TCE as anesthetic. Death, attributed to respiratory failure, occurred between .29 and .93 (avg=.60) ml/kg.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
216 Human LSE 12M	1 d 30 min/d	0, 250, 350, 450, 550	CS	Cardio	550 M			Gamberale and Hultengren 1973
Comments: Healthy human subjects exposed to increasing concentrations of 1,1,1-TCE in consecutive 30 min periods on one day (control 30 min periods on another day). No effect on heart rate.								
535 Human 1M	once	NS	GN HP CS OR					Guberan et al. 1976
Comments: Case report of a 20 year old man who intentionally inhaled 1,1,1-TCE. Vomiting was followed by ventricular fibrillation and dath. No lesions were found in the heart at autopsy.								
461 Human 1M	4 hr	NS	HP BC UR					Halevy et al. 1980
Comments: Case report of a man spraying with 1,1,1-TCE for 4 hours in an enclosed space without ventilation. Several hours after finishing the job, the patient became dizzy, with headache and nausea. Upon admission to the hospital the patient complained of dizziness, but was fully conscious with no neurological deficit or dyspnea. Liver toxicity was indicated by elevated serum bilirubin, SGOT, and LDH, which all gradually declined to normal 38 days later. A liver biopsy 14 days after exposure showed infiltration of portal spaces by lymphocytes, histocytes, neutrophils, and eosinophils, as well as cholestasis. Renal toxicity was indicated by proteinuria, elevated blood creatinine and reduced creatinine clearance. These changes were maximal at admission and disappeared 10 days later. The authors noted the atypical course of 1,1,1-TCE induced illness in this patient (minimal neurological effect, prominent liver and kidney toxicity) and suggest an individual hypersensitivity may be one explanation.								
516 Human 1M,1F	once	NS	OW GN HP					Hall and Hine 1966
Comments: This is a report of 2 cases, one a 29 year old man and the other a 19 year old woman, who apparently inhaled a lethal concentration of 1,1,1-TCE. The fatal concentrations were not estimated, although the woman had been sniffing cleaning fluid for several days, and the man had died with a rag soaked in cleaning fluid over his mouth. In the man, the weight of both lungs was markedly increased and edematous, the lungs and bronchi contained blood-tinged white frothy fluid, while the pulmonary parenchyma showed considerable congestion and edema with patchy hemorrhage. The kidney showed vascular congestion, and the blood contained 13.0 mg% 1,1,1-TCE (13 mg/100 mL). The woman's lungs were similar, with passive congestion throughout, and parenchyma with blood, frothy fluid. Microscopic examination revealed edema, and congestion of the pulmonary parenchyma with atelectasis in the woman. The blood concentration of the 1,1,1-TCE was 72 mg% (72 mg/100 mL).								

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
498 Human 1M	<1 hr	NS	GN CS					Jones and Winter 1983

to 1,1,1-TCE ?

Comments: This is a case report of a 17 year old man who was found unconscious after less than 1 hour of accidental inhalation exposure. The man had been cleaning the upholstery of a car, with one door of the car open for ventilation. A simulation of the circumstances of his death revealed a possible exposure concentrations of 6410 ppm at the location of the man's face upon discovery. The man was taken by ambulance to a hospital, and was discovered to be dead on arrival. Post-mortem revealed his bronchi to be blocked with vomitus. A small hemorrhage in the right lung was observed. No further observations were reported. Death suggest that unconsciousness occurred.

501 Human 1M	<2 hr	NS	GN BC CS					Jones and Winter 1983

Comments: This is a case report of a 20 year old man who died after less than 2 hours of inhalation exposure and probable concurrent dermal expsoure to 1,1,1-TCE while using the solvent as a degreasing agent. The concentration in the room was apparently not measured, although the room was noted to be "fume-filled," and solvent-induced dermal changes were observed on all exposed skin. Edema of the lungs, serous effusions in pleural cavities, and petechial hemorrhages on the pleural surface were noted at autopsy. Pericardial and gastric petechial hemorrhages were also observed, with gastric mucosal congestion. Blistering and second-degree chemical burns were evident on the face and neck, and changes were observed on exposed skin of the trunk. The solvent was detected in the blood, brain, and liver at 4.2 mg/100 mL, 123 mg/100 g, and an unreported concentration, respectively.

709 Human 1M	NS	NS	CS OF					Kelly and Ruffing 1993

Comments: This is a case of a 15-year-old admitted to the hospital after repetitively (unspecified) inhaling Scotchguard (1,1,1-TCE plus fluorocarbons). The main effect was acute eosinophilic pneumonia with respiratory failure. His condition rapidly reversed after administration of corticosteroids and he was removed from mechanical ventilation 60 hours after steroid administration. Pulmonary function tests at follow up were normal. The authors indicate that the clinical syndrome they observed had not been previously reported associated with volatile substance abuse.

513 Human 2M,2F	NS	NS	GN HP					King et al. 1985

Comments: This is a report of 4 cases of young adults (aged 13-18 years old) who intentionally sniffed TCF (liquid paper), which contains 1,1,1-TCE. The air concentration of the solvent was not estimated. TCF also contains trichloroethylene, among other constituents. All of the subjects collapsed suddenly within several hours of sniffing the TCF. Three showed either pulmonary blockage, fluid, or hemorrhaging. Two had heart anomalies, and 1 showed evidence of subcutaneous drug use. Three of the kids were physically exerting themselves when they collapsed. The circumstances of death suggest that they suffered from a fatal cardiac arrhythmia. The blood of 2 and the lung tissue of 3 were examined for the presence of 1,1,1-TCE, and were found to be positive in each case.

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
274 Human 1NS	1 d 30min/d	NS (ml/kg)	CS					Krantz et al. 1959
Comments: Anesthesia maintained for 30 minutes. No significant ECG changes. 70% decrease in blood pressure. Recovery slow. Subject complained of tiredness for several hours after.								
518 Human 3M	once	NS	GN CS					MacDougall et al. 1987
Comments: This is a report of 3 fatal cases of inhalation of 1,1,1-TCE in a thinning fluid (Tipp-Ex) in boys of 13-15 years of age. The air concentrations of the solvent, and other solvents in the thinner were not reported. Pulmonary congestion and edema were reported, as well as hemorrhaging and frothy fluid in the air passages and lungs, and inhalation of aspirated gastric contents. Blood concentrations of 1,1,1-TCE were 0.003, 0.2, and 7.4 æg/g blood.								
771 Human LSE 12M	Once 4 hr 1,1,1- ?	20, 200	BH CS BI Resp			200 M (nasal irritation)		Muttray et al. 1999 1,1,1-trichloroethane
Descriptions: Trichloroethane may act as a slight respiratory tract irritant, as evidenced by increased concentrations of proinflammatory cytokines in nasal secretions of 12 healthy volunteers exposed to 1,1,1-trichloroethane at a vapor concentration of 200 ppm for 4 hours.								
490 Human 1M	once	NS	CS					Northfield 1981
Comments: A young man of 15 years died on the job while degreasing small metal "parts" by running the solvent on the parts, over an open tank of 1,1,1-TCE. He was found slumped into the tank with his head touching the solvent. Subsequent investigation of the site of death revealed that when the solvent was not disturbed in the tank, air concentrations of 200, 6000, and >70,000 ppm were respectively recorded at 15 cm above the tank's rim, 8-15 cm below the tank's rim, and 8-15 cm above the surface of the solvent. When the solvent was disturbed, concentrations rose to 73,000 and 94,000 ppm at 8 cm above and 15 cm below the rim of the tank, respectively. The cause of death was reported to be cardiorespiratory failure.								
492 Human 1M	once	NS	CS					Northfield 1981
Comments: A young man of 16 years died after apparently intentionally sniffing 1,1,1-TCE on the job, as evidenced by an unspecified skin "reaction" around his mouth. Fellow employees had found him in a "stuporose" condition on 2 previous occasions. The normal exposure concentrations at his work station was reported to be 65 ppm, and 735 ppm with the ventilation system turned off. The cause of death was reported to be asphyxia.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
465 Human 1M	NS	NS	GN HP					Ranson and Berry 1986
Comments: This is a case report of a 13 year old boy who apparently had inhaled 1,1,1-TCE in an unknown mixture. Some congestion of the upper respiratory tract was the only finding after gross and histopathological examinations.								
477 Human 4M	once	NS	GN HP					Stahl et al. 1969
Comments: This is a case report of 4 men exposed by inhalation to 1,1,1-TCE in close, unventilated quarters. The air concentration was not reported. Edema and congestion of the lungs were observed at autopsy, and histological examination revealed localized polymorphonuclear leukocytes in the lungs. The skin of the buttocks showed bullous lesions and focal denudations, while histopathological examination revealed intraepithelial bullous changes. Tissue concentrations in the blood, brain, and liver ranged from 6-12 mg/100 mL, 50-59 mg/100 g, and 11-22 mg/100 g, respectively. of 1,1,1-TCE ?								
480 Human 1M	once	NS	GN HP					Stahl et al. 1969
Comments: This is a case report of a 20 year old man who had been exposed to 1,1,1-TCE in paint "remover" in a closed space for an unknown length of time. The air concentration was not reported. The man was found dead, and an autopsy was performed. At autopsy, congestion was observed in the liver, kidneys, and lungs, and the lungs were found to be moderately edematous upon microscopic examination. Tissue concentrations of the solvent in kidney, liver, and muscle were reported to be 2.4, 9.8, and 4.9 mg/100 g respectively.								
483 Human 1M	once	NS	GN HP					Stahl et al. 1969
Comments: This is a case report of a young man of 17 years who died while using 1,1,1-TCE in a small room, less than 7.75 hours after beginning the job. The air concentration of the solvent was not reported. Cyanosis of the skin was observed at autopsy. The liver and kidney were moderately congested and the lung showed "marked" edema. There was also evidence that gastric contents were aspirated. Tissue concentrations of the solvent in kidney, liver, muscle, and lung were reported to be 0.26, 0.49, 0.26, and 0.18 mg/100 g, respectively. Concentrations in blood and urine were reportedly 0.15 and 0.1 mg/100 mL, respectively.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
468 Human 1M	once	NS	OW GN HP BC CS OR HE					Travers 1974
Comments: This is a case report of an 18 year old man who apparently intentionally inhaled straight 1,1,1-TCE. The man was administered emergency care immediately upon collapsing, an unreported time after inhaling TCE. ECG revealed ventricular tachycardia, and he showed gross hematuria. Hypotension and bradycardia were progressive and cardiac arrest repeated until his death. The right and left lungs were congested, and weighed 600 and 800 g, respectively. Atrial and vetricular dialation were evident, with some vetricular subendocardial hemorrhage. No detectable TCE was evident in blood, brain, liver, and kidney tissues. WBC count was increased about 3 times over the normal level, serum potassium and chloride were decreased from normal, serum hemoglobin was slightly increased, and serum osmolality and pH were elevated.								
708 Human 1M	once	NS	CS OF					Wodka and Jeong 1991
Comments: This is a case of a 15-year-old boy who collapsed while sniffing typewriter correction fluid. The morning following arrival to the hospital myocardial injury was documented by abnormal electrocardiogram and abnormal echocardiogram. The patient was discharged 4 days after admission and his post-hospital course was unremarkable.								
469 Human 1M	NS	NS	BC CS OR					Wright and Strobl 1984
Comments: This is a case report of a 45 year old man who had experienced nearly continuous occupational inhalation exposure to 1,1,1-TCE (duration not reported), and routinely washed machine parts over an open bucket, occasionally dipping his arm in the solvent up to the elbos. He showed persistant ventricular arrhythmias and 20 æm/100 mL each of 1,1,1-TCE and 1,1,2-TCE in the urine after complete physical, hematological, serum chemistry, and urinalysis exams. Ventricular arrhythmias were persistant for 2 weeks after the last exposure to the solvent, during which time he was successfully treated with quinidine gluconate, and after which he was asymptomatic. He wore gloves and ventilation was improved thereafter, and he was asymptomatic 6 weeks later.								
258 Monkey 3B (Rhesus)	NS	.28 (ml/kg)	CS	Resp	0.28 (< oxygen uptake)			Krantz et al. 1959
Comments: Rhesus monkey anesthetized using 1,1,1-TCE. Oxygen uptake was depressed compared to pre-exposure values. The degree of depression was similar to that caused by chloroform.								

Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Inhalation

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
39 Rat LSE 10-36B (Wistar)	Once 6-420 min	8000, 10000, 12000, 15000, 18000, 30000	BW	Bd Wt	30000			Adams et al. 1950
Comments: No change in body weight after exposure to 30,000 ppm 1,1,1-TCE ? for 6-12 minutes or lower concentrations for longer periods.								
41 Rat LSE 3-5M (Wistar)	Once 6-420 min	0, 8000, 12000, 18000	OW GN HP BW	Resp	18000 M			Adams et al. 1950
				Cardio	18000 M			
				Hepatic		8000 M (Increased liver weight, mild fatty change)		
				Renal	18000 M			
				Bd Wt	18000 M			
Comments: 17 rats served as controls. Animals were killed and examined 24 hr after exposure to 1,1,1-TCE ? In liver, slight increase in relative liver weight and mild fatty changes after 8000 ppm for 7 hrs; more severe fatty changes and more increase in weight after 12,000 ppm for 7 hrs; no effect after 18,000 ppm for 2 hrs. Fatty changes considered to be reversible; no necrosis seen in liver. In kidney, slight increase in relative weight after 12000 ppm for 7 hr and 18000 ppm for 2 hr, but no histological effects (not considered adverse. No change in body weight.								
125 Rat 12M (Sprague-Dawley)	1 d 6 hr/d	10000-11000	GN BW	Resp	11000 M			Bonnet et al. 1980
				Hepatic	11000 M			
				Renal	11000 M			

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
				Bd Wt	11000 M			
Comments: 1,1,1-TCE 92.6% pure. Gross necropsy of survivors on 14th day showed no macroscopic lesions of liver, lung or kidney. Body weight also unaffected.								
128 Rat LSE 5M (NS)	1 d 2 hr/d	0, 11600, 13070	OW BC BI	Hepatic	13070 M			Carlson 1973
Comments: No effect on relative liver weight, liver glucose-6-phosphatase, SGPT, or SGOT (measured 22 hr post exposure). Pretreatment with 3-methylcholanthrene had no effect. Pretreatment with phenobarbital potentiated TCE hepatotoxicity: increased relative liver weight, decreased glucose-6-phosphatase, and increased SGOT and SGPT 4-6 times over controls. Phenobarbital alone had no effect.								
401 Rat 6M (Sprague-Dawley)	1 d 4-6 hr/d	0, 5000, 10000	HP BC	Resp	10000 M			Cornish and Adefuin 1966
				Hepatic	10000 M			
				Renal	10000 M			
				Endocr	10000 M			
Comments: Sprague-Dawley rats were used. They were sacrificed 24 hours after the end of the exposure to 1,1,1-TCE ? No effects on SGOT, SGPT, or serum isocitric dehydrogenase (SICD) were observed. No histopathological changes in the lungs, liver, kidneys, or adrenals were observed. Pre-treatment with ethanol (5 g/kg by gavage in water) 18 hours before exposure did not affect these results.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
403 Rat LSE 6M (Sprague-Dawley)	1 d 2 hr/d	0, 10000, 15000	HP BC CS	Resp	15000 M			Cornish and Adefuin 1966
				Hepatic	15000 M			
				Renal	15000 M			
				Endocr	15000 M			
				Bd Wt	15000 M			

Comments: Rats were sacrificed 24 or 48 hours after the end of the exposure to 1,1,1-TCE ?. There was no effect on body weight. No effect on SGOT, SGPT, or serum isocitric dehydrogenase (SICD) was observed. No histopathological changes in the lungs, liver, kidneys, or adrenals were observed. Pre-treatment with ethanol (5 g/kg by gavage in water) 18 hours before exposure did not affect these results.

248 Rat LSE 10M (Sprague-Dawley)	1 d 24 hr/d	0, 2500- 3000	CS BI OF	Hepatic	2500 M			Fuller et al. 1970

Comments: Rats were exposed to reagent grade 1,1,1-TCE. TCE reduced the duration of narcosis (loss of righting reflex) produced by hexobarbital, zoxazolamine, or meprobamate. Neither pretreatment with morphine nor adrenalectomy had any effect, indicating reduced narcosis not due to stress. Reduced narcosis attributed to increased drug metabolism. TCE produced increases in hexobarbital metabolism, zoxazolamine metabolism, aminopyrine demethylation, NADPH cytochrome C reductase, and CO-binding pigment (P-450). There was no effect on liver microsomal protein. Liver weight was increased. Pretreatment with cycloheximide or actinomycin D (inhibitors of protein synthesis) blocked the effects of TCE. The increase in drug-metabolizing enzymes after TCE inhalation consisted of an induction of new enzyme protein. Not considered an adverse effect.

140 Rat LSE 6M (Wistar)	10 d 24 hr/d	0, 200, 400, 800	BW OW BC BI	Hemato	800 M			Koizumi et al. 1983

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
				Hepatic	800 M			
Comments: Wistar rats exposed to 99.95% pure 1,1,1-TCE. Increased activity of mixed function oxidase system (MFOS) and increased liver weight at 200 ppm (not considered adverse). Effect greater at 200 ppm than higher concentrations (dose-effect relationship not well established). No effect on SGPT or RBC/WBC counts. Phenobarbital potentiated the TCE effects on MFOS activity and liver weight. Pretreatment with cyclohexane oxide did not alter TCE effect on MFOS activity, indicating epoxide hydratase not involved in TCE metabolism. These results suggest TCE oxidized by MFOS, but epoxide hydratase not involved.								
141 Rat 8M (Wistar)	2 d 24hr/d	0, 50, 400, 800	BC	Hepatic	800 M			Koizumi et al. 1984
Comments: Wistar rats were exposed to 99.95% pure 1,1,1-TCE. The activity of δ-aminolevolenic acid dehydratase (δ-ALA-D) in liver and blood was examined. There was no inhibition of δ-ALA-D activity in liver. Slight decrease in δ-ALA-D activity in blood (to 85% of control) at 800 ppm (considered negligible by authors).								
256 Rat 4NS (NS)	3,6 or 9 d 1hr/d	NS	GN HP					Krantz et al. 1959
Comments: Rats repeatedly anesthetized with 1,1,1-TCE. No significant pathological effects in the kidney or liver, except liver necrosis in 1 rat after 9 exposures. Not enough information to say if effect was compound-related.								
257 Rat 4-6NS (NS)	1 d 1hr/d	NS	OF					Krantz et al. 1959
Comments: Rats were anesthetized with 1,1,1-TCE and the heart was removed. 33% reduction in oxygen uptake of myocardium compared to control rats. Similar to result for chloroform. Authors consider this change significant.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
185 Mouse 5F (NS)	1 d 3hr/d	800	BC BI	Hepatic	800 F			Takahara 1986a
Comments: Study reports very slight decreases in liver ATP level and plasma triglyceride (TG) level, increase in liver triglyceride level, and mild increase in SGPT. No concurrent controls were included in the experiment and no statistical analysis was performed; only the increase in liver TG seems like clear effect. Author hypothesizes that decrease in liver ATP inhibits lipoprotein synthesis and inhibits release of TG from liver; TG then accumulates in liver and is reduced in plasma; these changes accompanied by damage to liver cell, which liberates GPT into blood.								
752 Dog 6M (Mongrel)	1x 3 min (IT)	10,000		Cardio		10000 M (decreased blood pressure)		Aoki et al. 1997 1,1,1-trichloroethane
Calculations: 1% v/v = 10,000 ppm								
Descriptions: Six adult male mongrel dogs were anesthetized and exposed to 1v/v% (10,000 ppm) of 1,1,1-TCE via tracheal intubation for 3 minutes. Systemic arterial pressure (SAP), pulmonary arterial pressure (PAP), and central venous pressure (CVP) were recorded with femoral arterial lines and floating balloon thermodilution catheters. Cardiac output (CO) and pulmonary capillary wedge pressure (PCWP) prior to exposure and at 0, 5, 15, 30, and 60 minutes after exposure.								
Results: mSAP decreased significantly against the baseline value after exposure, but was not significantly decreased 5 minutes after exposure. mPAP at the end of exposure increased significantly. There were also significant differences from the baseline value at 5, 15 and 30 minutes after exposure with a gradual trend returning to the baseline value. There was no significant change in PCWP or CO after exposure against the baseline value.								
228 Dog LSE 4-7NS (Beagle)	1 d 5 min/d	NS	CS	Cardio			7500 (EC50 for cardiac sensitization)	Clark and Tinston 1973
Comments: Beagles exposed using face mask. Adrenaline (5 æg/kg) administered at end of exposure and 10 minutes post-exposure. EC50 for cardiac sensitization at end of 5 minutes exposure was 7500 ppm (95% CI: 4000-11000 ppm). 50% of animals sensitized to adrenaline. Only serious arrhythmias (e.g. multifocal ventricular ectopic beats, ventricular fibrillation) counted. No arrhythmias without adrenaline. No arrhythmia from post-exposure adrenaline. Cardiac sensitization apparently transitory, probably no damage to heart cells. Authors feel cardiac sensitization probably structurally non-specific and an example of physical toxicity.								

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Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Inhalation

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
253 Dog LSE 6M,6F (Beagle)	1 d 15 min/d	0, 5000, 10000	CS	Cardio	10000			Egle et al. 1976
Comments: Static exposure of unanesthetized beagles. Used Scotchguard (SG) and mixture of pure 1,1,1-TCE with Freon 12 (measured to give concentrations of 5000 or 10,000 ppm 1,1,1-TCE in air). Same dogs tested at all concentrations; pre-exposure values used as controls. Heart rate measured by ECG - mild increase in heart rate from SG (5000 ppm TCE) with/without epinephrine, but no effect from SG (10,000 ppm TCE). Pure TCE had no effect at either concentration. Authors conclude change probably not due to treatment. No cardiac sensitization in this study. SG (5000 ppm TCE) with/without 8 æg/kg epinephrine did not produce cardiac arrhythmias. SG (5000 ppm TCE) with 16 æg/kg epinephrine produced severe arrhythmias, but so did the epinephrine alone. Neither SG (10,000 ppm TCE) nor pure TCE at either concentration produced arrhythmias with or without epinephrine.								
271 Dog LSE 9NS (NS)	1 d 5 min/d	0, 8000, 15000, 20000, 25000	GN CS HP	Resp	25000			Herd et al. 1974
				Cardio			8000 (50 mm Hg reduction in mean blood pressure)	
				Hepatic	25000			
Comments: Mongrel dogs anesthetized with pentobarbital or chloralose pentobarbital and exposed to 97.5% pure 1,1,1-TCE. 5 minute exposure periods (1 hour apart) to increasing concentrations. No histological effects in lungs or livers of dogs that died from blood pressure depression during exposure (other organs examined not specified). Concentration-dependent decrease in blood pressure. At lower concentrations (8000, 15000 ppm), parallel decline in systolic and diastolic pressure accompanied by increases in cardiac output (heart rate and stroke volume) and myocardial contractility. Decline in blood pressure at these concentrations due to marked decrease in total peripheral resistance. At higher concentrations (20000, 25000 ppm), reductions in cardiac output and myocardial contractility produced blood pressure decline, and peripheral resistance not altered (indicates maximum peripheral vasodilation during initial phase). Effect on arterial pressure reversed by stopping exposure (recovery within 15 min). Myocardial factors (heart rate, stroke volume) required 45 min to recover after exposure. No spontaneous arrhythmias seen. Authors feel these results, and the fact that blood pressure did not decline when B-blockade given, suggest reflex stimulation of heart. Effects cannot be ascribed to general CNS depression.								
273 Dog 1-4NS (NS)	1 d up to 60 min/d	.34 (ml/kg)	CS OF	Cardio		0.34 (< blood pressure)		Krantz et al. 1959
				Hemato	0.34			

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
701 Human 1M	once	NS	GN					Stahl et al. 1969
Comments: This is a case report of a young man age 17 yr who died while using 1,1,1-TCE in a small room, less than 8 hours after beginning the job. The air concentration of the solvent was not reported. There was moderate congestion in the spleen.								
702 Human 1M	once	NS	GN					Stahl et al. 1969
Comments: This is a case of an obese 24 year old man who died after inhaling an unknown concentration of 1,1,1-TCE for less than 2 hours. At autopsy, spleen congestion was observed.								
703 Rat 6M (Sprague-Dawley)	1 d 4-6 hr/d	0, 5000, 10000	GN HP		10000 M			Cornish and Adefuin 1966
Comments: Rats were sacrificed 24 hours after the end of exposure. There were no gross or histopathological changes in the spleen. Pre-treatment with ethanol (5 g/kg by gavage in water) 18 hours before exposure did not affect the results.								
704 Rat LSE 6M (Sprague-Dawley)	1 d 2 hr/d	0, 10000, 15000	GN HP		15000 M			Cornish and Adefuin 1966
Comments: Rats were sacrificed 24 or 48 hours after the end of exposure. There were no gross or histopathological changes in the spleen. Pre-treatment with ethanol (5 g/kg by gavage in water) 18 hours before exposure did not alter the results.								

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Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Inhalation

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
276 Human LSE 50NS	1 d up to 2 hr/d	10000- 26000	CS				10000 (anesthesia)	Dornette and Jones 1960
Comments: Patients of varying health anesthetized with 1,1,1-TCE in nitrous oxide and oxygen mixture. Induction of anesthesia from 10,000-26,000 ppm extremely rapid (within 2 min of start). Maintenance of light anesthesia from 6,000-22,5000 ppm. Authors speculate that 1/4 of total narcosis attributable to nitrous oxide; effect without nitrous oxide unknown. Recovery rapid (within 5 minutes).								
508 Human 2M	<45 min	NS	CS OR					Droz et al. 1982
Comments: This is a report of 2 cases chosen to illustrate sudden death in men following intentional inhalation of 1,1,1-TCE. Simulations of the fatal air concentrations showed between 6,000 and 20,000 ppm of the solvent. One man was spasmotic and the other collapsed suddenly after vomiting before emergency professional help arrived. Cerebral death was diagnosed in 1 case.								
215 Human LSE 12M	1 d 30 min/d	0, 250, 350, 450, 550	CS OF		250 M	350 M (increased reaction time, decreased perceptual speed and manual dexterity)		Gamberale and Hultengren 1973
Comments: Healthy human subjects exposed to increasing concentrations of 1,1,1-TCE in consecutive 30 minute periods on one day (control 30 minute periods on another day). 5 performance tests during each 30 min exposure period: manual dexterity with wire spiral, perceptual speed with identical numbers, perceptual speed with spokes, simple reaction time, and choice reaction time. Subjective assessment from test subjects not affected by exposure. Statistically significant reduction in performance in all tests (at 250 ppm for identical number test; at 350 ppm for other tests). Percent decrease in performance appeared to be concentration-dependent. Authors conclude 1,1,1-TCE has detrimental effect on human psychophysiological function after relatively brief exposure period.								
471 Human 1M	once	NS	OW GN HP					Gresham and Treip 1983
Comments: This is a case report of an 18 year old man who entered a coma after being discovered with his head in a puddle of methyl chloroform. The coma lasted for at least 3 years before the man died. The air concentration during exposure was not estimated. The man was found with fixed, dilated pupils that were unresponsive to light. Cardiopulmonary activity was resuscitated about 15 minuts later. A possible lesion of the occipital cortex was indicated by absence of the protective eye reflex. During his coma, restlessness and jerking of limbs gave way to fixed flexion of all four limbs. Cerebral atrophy indicating cerebral apoxia was evident in a CAT scan performed 2 months into his coma, and confirmed at autopsy. The brain was small (1112 g) at autopsy.								

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Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Inhalation

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
184 Human 4-5M	1 d 4hr/d	0, 200, 400	CS OF		400 M			Savolainen et al. 1981
Comments: Healthy humans exposed to technical grade 1,1,1-TCE. Same subjects exposed to different concentrations on different days. Psychophysiological tests before, during, and after exposure. No effect on body sway, tapping speed, or critical flicker fusion threshold. Exposure to low concentrations slightly shortened reaction time, but exposure to high concentrations prolonged reaction time (afternoon only). No nystagmus produced. Authors conclude no marked impairment of psychophysiological function in this study. They suggest TCE may have biphasic pattern of effects on CNS: slight stimulation at lower concentrations, and depression at higher concentrations (like alcohol). This suggestion based on weak evidence (reaction-time data). No synergistic or antagonistic interaction with xylene.								
520 Human 25M	once	NS	CS					Silverstein 1983
Comments: This is a case report of an industrial spill of at least 1.5 gallons of 1,1,1-TCE that initially affected 2 men, and then at least 23 rescuers. The estimated air concentration at the initial spill was about 9000 ppm. One man was "overcome," and 3 others of the 25 involved lost consciousness.								
476 Human 4M	once	NS	GN HP					Stahl et al. 1969
Comments: This is a case report of 4 men exposed by inhalation to 1,1,1-TCE in close, unventilated quarters. The air concentration was not reported. Four out of 4 men became unconscious, and 3 subsequently died.								
479 Human 1M	once	NS	GN HP					Stahl et al. 1969
Comments: This is a case report of a 20 year old man who had been exposed to 1,1,1-TCE in paint "remover" in a closed space for an unknown length of time. ~~Ath~~ air concentration was not reported. The man was found dead, and an autopsy was performed. Congestion of the brain as well as microscopic changes suggesting anoxia were observed at autopsy. Further analysis revealed a lactic acid concentration in the brain of 283 mg/100 g. The concentration of the solvent in brain tissue was reported to be 2.7 mg/100 g. u								
482 Human 1M	once	NS	GN HP					Stahl et al. 1969
Comments: This is a case report of a young man of 17 years who died while using 1,1,1-TCE in a small room, less than 7.75 hours after beginning the job. The air concentration of the solvent was not reported. At autopsy, the brain was moderately congested, with a lactic acid concentration of 226 mg/100 g, and a solvent concentration of 0.32 mg/100 g.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
124 Rat LSE 12M (Sprague-Dawley)	1 d 6 hr/d	10000-11000	CS				10000 M (all somnolent)	Bonnet et al. 1980
Comments: All rats appeared somnolent during exposure. Hypotonia was also reported. 1,1,1-TCE was 92.6% pure.								
372 Rat 5M,5F (CDF)	1 d 6hr/d	0, 5000	BW GN				5000 (motor incoordination)	Calhoun et al. 1981
Comments: Male and female CDF rats (Fischer 344 derived) received a single exposure to 5000 ppm 1,1,1-TCE for 6 hours and observed for 2 days before sacrifice. Rats were evaluated for clinical signs of toxicity and gross pathology. Rats showed motor incoordination from 1.5 hours of exposure to termination of exposure after which they quickly recovered (15 min). Pathology results ?								
420 Rat 5M,5F (Fischer 344)	1 d 4 hr/d	15000, 18000, 22000	BW GN CS				15000 (ataxia and hypoactivity)	Calhoun et al. 1988
Comments: Fischer 344 rats were exposed to Aerothene TT (94.5% 1,1,1-TCE, 5.5% inhibitors). There was a two-week observation period. During exposure rats became uncoordinated, lethargic, and then unresponsive. 3/5 females died at 18,000 ppm and all 10 rats died at 22,000 ppm (deaths during exposure). Survivors appeared normal after day 2 of the study. Body weights decreased during the first week of observation, but recovered during the second week. Necropsy revealed facial soiling and congestion of visceral organs in rats that died. No lesions were seen in the survivors.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
130 Rat LSE 6B (Alderley Park)	1 d 10-15 min/d	NS	CS				5000 (EC50 for ataxia)	Clark and Tinston 1982
Comments: EC50 for CNS depression (ataxia, loss of righting reflex) was 5000 ppm after 10 min exposure to Alderley Park rats (95% CI: 4,000-6,000 ppm). EC50 calculated by Thompson method. CNS effects rapidly reversed on cessation of exposure (indicates rapid elimination from body). Authors feel effect on CNS is probably structurally non-specific, i.e. toxicity not from combining with specific target, but just from being in cell and temporarily disorganizing its function. According to this theory there should be no permanent structural damage to brain.								
209 Rat LSE 6M (Wistar)	1 d 5-60 min/d	0, 8000	BI			8000 M (Increased brain lactate and pyruvate)		Folbergrova et al. 1984
Comments: Wistar SPF rats anesthetized with N2O. Highly significant increase in tissue concentrations of lactate and pyruvate in the brain, which indicates either stimulus of glycolysis or inhibition of pyruvate oxidation. Increase in concentrations of citric acid cycle intermediates suggests enhanced pyruvate carboxylation. Slight reduction in cAMP; no effect on cGMP. These effects all found right after 5 or 60 min exposure, but not 60 min later, indicating quick recovery.								
224 Rat LSE 6-11M (Wistar)	1 d 0.5-2 hr/d	0, 3500, 6000, 7800	CS BI		3500 M	6000 M (dizzness, decrease local cerebral glucose consumption)	7800 M (ataxia)	Hougaard et al. 1984
Comments: Unanesthetized Wistar SPF rats used. Unequivocal intoxication in all exposed animals at 6000 ppm. Ataxic within 10 minutes at 7800 ppm. Local cerebral blood flow (measured using radioisotopes) significantly increased by 28 to 45% in 11 of 23 brain regions following 30 minutes exposure to 6000 ppm. Local cerebral glucose consumption (measured using [14C] deoxyglucose) significantly decreased by 21-56% in 10 of 23 brain regions following 60 min exposure to 6000 ppm. Largest decreases were in inferior colliculus and substantia nigra. In rats anesthetized with N2O and exposed to 7400 ppm 1,1,1-TCE for 60 minutes, cerebral blood flow increased in all 23 brain regions and EEG showed generalized slower activity.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
785 Rat LSE 5M (Sprague-Dawley)	40 or 100 min	0, 5000	BI			5000 M (reduced cGMP in the brain)		You and Dallas 2000 1,1,1-trichloroethane
Descriptions: Groups of male Sprague-Dawley rats (5 per group) were exposed to 1,1,1-trichloroethane at a vapor concentration of 5000 ppm for 40 or 100 minutes. Controls were exposed to clean air for 40 minutes. Immediately following the termination of exposure, the rats were sacrificed and representative samples of various brain regions were prepared for assay of cyclic GMP (glucose monophosphate) levels.								
Results: The cGMP levels in the cerebellum of the rats exposed to 1,1,1-trichloroethane for 40 minutes were greater than 50% lower than those of controls. Exposure for 100 minutes resulted in an even greater decrease in cerebellar cGMP levels. Smaller decreases were observed in the cortex.								
210 Mouse LSE 8M (CD-1)	1 d 20 min/d	0, 1000, 2000, 4000, 8000	CS OF				2836 M (EC50 for effect on operant behavior)	Balster et al. 1982
Comments: CD1 mice exposed to inhibited 1,1,1-TCE in dynamic exposure system. Mice trained to lever press on an operant schedule for water reinforcement. Same mice exposed at all test concentrations (including control). All mice maintained steady baseline throughout study (3 control sessions) - also checked before exposure to see if on baseline that day, and after exposure to judge recovery. Baseline different for each mouse so results reported as average percent of control. There was a concentration-dependent decrease in response rate (EC50=2836 ppm with 95% CI=2042-3631 ppm). Complete suppression of response at 8000 ppm. No gross behavioral effects except motor stimulation at 8000 ppm. Concentration-dependent increase in recovery time, from 5 minutes at 1000 ppm to 14 minutes at 8000 ppm. This study found a readily reversible concentration-dependent decrease in response rate. Authors conclude operant behavior appears to be sensitive to effects of 1,1,1-TCE in mice.								
753 Mouse LSE 9-10 M (CFW)	30 min	500; 1250; 2,500; 5,000; 7,500; 10,000; 12,500	CS			1250 M (increased motor activity)		Bowen and Balster 1996
Descriptions: Ten naive male mice were monitored for motor activity for 30 minutes, once per day (Monday-Friday) for one week. During the following weeks, motor activity of the mice was monitored for 30 minutes per workday. On Tuesdays and Fridays, motor activity was monitored during single 30-minute exposures to 1,1,1-trichloroethane at randomized graded concentrations of 500; 1250; 2,500; 5,000; 7,500; 10,000; or 12,500 ppm in a static system. Nine other male mice were similarly tested in a dynamic system 500; 1250; 2,500; 5,000; 7,500; or 10,000 ppm.								
Results: LOAELs for statistically significantly increased motor activity were 1,250 and 2,500 ppm for dynamic and static exposures, respectively. The 1,250 ppm exposure level in the dynamic system was the only concentration that resulted in significantly increased motor activity; the 10,000 ppm level in this system resulted in significantly decreased motor activity. In the static system, exposure concentrations of 2,500; 5,000; and 7,500 ppm resulted in significantly increased motor activity. Activity at higher exposure levels was not significantly different from activity measured without 1,1,1-trichloroethane exposure.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
214 Mouse LSE 10M (Swiss OF1)	1 d 4 hr/d	0, 2064, 2525, 3119, 3569	CS OF				2064 M (altered swimming behavior)	De Ceaurriz et al. 1983
Comments: Swiss OF1 mice given 99% 1,1,1-TCE by dynamic exposure. "Behavioral despair" swimming test used (put mouse in water in restricted space and record duration of immobility during first 3 minutes). Controls try to escape during first minute, but immobile by third minute. There was concentration- dependent reduction in the duration of immobility (from 32% to 74%), which became significant at 2064 ppm. ID50 (concentration associated with 50% decrease in total duration of immobility) was 2729 ppm (95% CI = 2295-3191 ppm). Decreased duration of immobility was due to prolongation of escape activity, which may result from nonspecific action. Authors conclude this test provides a sensitive way to evaluate early signs of toxicity.								
710 Mouse LSE 10M (CFW Swiss)	4 d 24 hr/d	0, 500, 1000, 2000, 4000	CS				500 M (decreased threshold to convulsions upon withdrawal)	Evans and Balster 1993
Comments: Mice were exposed to 1,1,1-TCE continuously under dynamic conditions. Mice became sedated during exposure to 4000 ppm. Handling-induced convulsions developed after exposed ceased. The frequency and intensity of the convulsions was concentration-dependent. Two-four hours postexposure the percentage of mice having convulsions was 80% at 2000 ppm, but only 50% at 500 ppm. Exposure to 1,1,1-TCE also increased the susceptibility to pentylenetetrazol-induced convulsions. Reexposure to 1,1,1-TCE during the withdrawal period reduced the frequency and severity of the convulsions. Exposure to toluene, or injections of ethanol, midazolam, and pentobarbital also decreased the withdrawal effects. However, the anticonvulsant drugs chlorpromazine and phenytoin were without effects, suggesting that the reversal of 1,1,1-TCE withdrawal effects can be accomplished only by CNS depressants.								
135 Mouse LSE 8-135F (Swiss Webster)	1 d 10-780 min/d	13500	CS				13500 F (unconsciousness)	Gehring 1968
Comments: Swiss Webster mice exposed to 99.5% pure 1,1,1-TCE. ET50 for unconsciousness was 16.3 minutes (95% CI: 15.4-17.2 min).								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
173 Mouse LSE 1-4M (CD-1)	1 d 20 min/d	0, 125, 250, 500, 1000, 2000, 4000, 8000, 10000, 12000, 14000	CS OF				850 M (EC50 for effect on ability to discriminate from ethanol)	Rees et al. 1987b

Comments: CD-1 mice exposed to inhibited 1,1,1-TCE. Same mice tested at each concentration. Mice trained to discriminate injections of ethyl alcohol (ETOH) from saline in 2 lever operant task. Concentration-dependent increase in pressing of ETOH lever (EC50=850 ppm), indicating ETOH effect generalized to TCE (actually the effect was biphasic and the number of ETOH responses decreased to very few at the highest 3 TCE concentrations; reason for this unknown, but may be due to disruption of stimulus control). There was also a concentration-dependent decrease in rate of responding (EC50=5360 ppm). Results suggest TCE shares discriminative-stimulus properties with ETOH (produces an intoxication similar to ETOH). ?

212 Mouse LSE 12M (CD-1)	1 d 30 min/d	0, 3600-23000	CS OF				5173 M (EC50 for impaired screen climbing ability)	Woolverton and Balster 1981

Comments: CD-1 mice exposed to 1,1,1-TCE inhibited with 3% dioxane. Observed stimulation of motor activity at lower concentrations. Ataxia followed by anesthesia and death (apparently due to acute respiratory depression) at higher concentrations. Mice trained to climb to top of inverted screen within 1 minute. Recorded percent of mice that could not climb the screen at 1, 5, 30, and 60 minutes after the end of exposure. EC50 for impaired screen-climbing at 1 minute post-exposure was 5173 ppm (95% CI: 4644-5778 ppm). At 7000 ppm (highest concentration used for behavioral test), half the mice recovered within 5 minutes and all recovered within 60 minutes. Some mice given ethanol by gavage 30 min before TCE exposure; the EC50 and LC50 were reduced in these animals. Ethanol potentiated effects of TCE at some concentrations; effects just additive at others. Authors conclude inverted screen test is sensitive measure of behavioral effects. 161

786 Mouse LSE 5M (CD-1)	40 or 100 min	0, 5000	BI			5000 M (reduced cGMP in the brain)		You and Dallas 2000 1,1,1-trichloroethane

Descriptions: Groups of male CD-1 mice (5 per group) were exposed to 1,1,1-trichloroethane at a vapor concentration of 5000 ppm for 40 or 100 minutes. Controls were exposed to clean air for 40 minutes. Immediately following the termination of exposure, the mice were sacrificed and representative samples of various brain regions were prepared for assay of cyclic GMP (glucose monophosphate) levels.

Results: The cGMP levels in the cerebellum of the mice exposed to 1,1,1-trichloroethane for 40 minutes were greater than 50% lower than those of controls. Exposure for 100 minutes resulted in an even greater decrease in cerebellar cGMP levels. Smaller decreases were observed in the cortex and medulla oblongata. ?

Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Inhalation

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE								
Developmental								
358 Rat LSE 30F (CD)	Gd 6-15 4 hr/d	0, 1000, 3000, 6000	BW OW FI WI HP CS FX MX DX TG		3000 F	6000 F (decreased female fetal weight, delayed ossification)		BRRC 1987a
Comments: Female CD rats were exposed to 1,1,1-TCE during gestation days 6-15 and observed for maternal toxicity and fetal developmental toxicity. Maternal toxicity parameters investigated were gestational and post-gestational body weight gain, food and water consumption, and gross necropsy. Developmental parameters included implants/litter, preimplantation loss, viable implants, resoprtions, live/dead fetuses, sex ratio, fetal body weight gain, and type and incidence of malformations. Maternal body weight gain was significantly reduced during exposure at 3,000 and 6,000 ppm and post-exposure (days 15-21) at all exposure levels. Maternal food consumption was significantly reduced at all exposure levels. Maternal water consumption was significantly increased at 6,000 ppm. Hypoactivity and perioral wetness during exposure were the only clinical signs of toxicity among the pregnant rats. There were no significant differences between control and 1,1,1-TCE exposed groups of rats regarding implants/litter, preimplantation loss, viable implants, resorptions, live/dead fetuses, or sex ratio. Female fetal body weight was significantly reduced in the 6000 ppm exposure group but neither male fetal body weight nor total fetal body weight were decreased. Out of 109 skeletal variations observed in all groups, control and exposed, only delayed ossification of the cervical centrum was significantly increased in the 1,1,1-TCE-exposed group (6,000 ppm only). 1,1,1-TCE appears to be slightly fetotoxic in rats at 6,000 ppm, however, the increased incidence of delayed ossification is common to rats that are exposed to many chemicals and is most likely related to maternal toxicity and not a direct chemical effect on the fetus.								
114 Rat LSE 23-30F (Sprague-Dawley)	Gd 6-15 7 hr/d	0, 875	BW OW FI FX MX TG		875 F			Schwetz et al. 1975
Comments: Sprague-Dawley rats exposed to Chlorothene VG (94% 1,1,1-TCE). About half the fetuses were examined for soft tissue abnormalities and half for skeletal abnormalities; 1 was given microscopic examination. No effect on maternal body weight, food consumption or relative liver weight. No effect on average number of implantations per litter, litter size, incidence of fetal resorptions, fetal sex ratios, or fetal body measurements. No effect on incidence of fetal soft tissue or skeletal abnormalities, or microscopic abnormalities. Authors conclude no maternal, embryonal, or fetal toxicity and no teratogenicity at concentration tested.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
INTERMEDIATE EXPOSURE								
164 Gn Pig 15NS (Hartley)	6 wk 5 d/wk 8 hr/d	0, 2210	CS					Prendergast et al. 1967

superCript ?

Calculations: 12060 mg/m3 x 24.45 x 1/133.4 = 2210 ppm.

Comments: Hartley guinea pigs exposed to 92% pure 1,1,1-TCE. Test animals compared to 314 controls from the 90-day study. No mortality reported.

20 Gn Pig 8M,8F (NS)	6 mo 5d/wk 7hr/d	0, 500	CS					Torkelson et al. 1958

Comments: Guinea pigs exposed to Chlorothene (94-97% 1,1,1-TCE). Concentration checked repeatedly, and was always within 10% of stated value. No effect on mortality.

33 Gn Pig 5F (NS)	3 mo 5d/wk 3-180min/d	0, 1000, 2000	CS					Torkelson et al. 1958

Comments: Guinea pigs exposed to Chlorothene (94-97% 1,1,1-TCE). Concentration checked repeatedly, and was always within 10% of stated value. No effect on mortality.

154 Dog 2NS (Beagle)	90 d 24 hr/d	0, 140, 380	CS					Prendergast et al. 1967

Calculations: 754 mg/m3 x 24.45 x 1/133.4 = 140 ppm; 2059 = 380 ppm.

Comments: Beagle dogs exposed to 92% pure 1,1,1-TCE. Test animals compared to 34 controls. No mortality reported.

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
INTERMEDIATE EXPOSURE								
				Bd Wt	2000 M			
Comments: Sprague-Dawley rats were exposed to industrial grade 1,1,1-TCE alone or in combination with noise of 2-40 kHz and 90 dB. No effects were seen on body weight, urine parameters, relative kidney weight, or the cytochrome P450 content of microsomal protein. The group that received 1,1,1-TCE alone had increased 3,4-dihydroxyphenylglycol (DHPG) concentration in the urine (DHPG is the main urinary metabolite of endogenous cathecholamines in the rat). They also had increased liver microsomal protein content which indicates a proliferation of liver endoplasmic reticulum. The animals that were exposed to both TCE and noise showed an increase in relative liver weight and liver microsomal monooxygenase activity. The experiment was repeated using pure 1,1,1-TCE, and no significant effects were seen. The authors conclude that additives or impurities were responsible for the effects noted.								
368 Rat LSE 28M,28F (CDF)	90 d 5 d/wk 6 hr/d	0, 150, 500, 1000, 2000	BW GN HP BC CS BI OR UR	Resp	1000	2000 (mild nasal epithelial degeneration)		Calhoun et al. 1981
				Cardio	2000			
				Gastro	2000			
				Hemato	2000			
				Musc/skel	2000			
				Hepatic	1000	2000 (reduced glycogen, fatty change)		
				Renal	2000			
				Dermal	2000			
				Ocular	2000			

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
INTERMEDIATE EXPOSURE								
				Bd Wt	2000			

Comments: Male and female CDF rats (Fischer 344 derived) were exposed to 1,1,1-TCE for 90 days, 5 days/week, 6 hours/day. Rats were evaluated for body weight, clinical signs of toxicity, clinical chemistry, hematological profile, urinalysis, and gross organ lesions. Except for the liver, lungs, kidneys, esophagus, trachea, and nasal turbinates, which were examined in all exposure groups, comprehensive histological examinations were performed on rats in the control and 2,000 ppm group. Eight rats at each exposure level were used for measurements of hepatic microsomal enzyme activity, and hepatic DNA synthesis and DNA content. Comprehensive histological examination revealed no lesions of major organs or tissues except the nasal turbinates and the liver. Mild nasal olfactory epithelium degeneration was noted in the 2,000 ppm exposure group. Minimal cytoplasmic microvacuolation suggestive of fatty changes were observed in the livers of 2/10 female rats exposed to 2000 ppm at an interim sacrifice at 45 days. Decreased size of centrilobular hepatocytes with increased variability of cytoplasmic staining and size, suggestive of reduced glycogen, was seen in both sexes of rats exposed to 2,000 ppm at the terminal sacrifice.

409	Rat	30 d 5 d/wk 7 hr/d	0, 1000	BW OW GN HP BC CS	Resp	1000		Dow Chemical Company 1969
	10M,10F							
(NS)								
					Cardio	1000		
					Hemato	1000		
					Hepatic	1000		
					Renal	1000		
					Bd Wt	1000		

Comments: 1,1,1-TCE contained 3% dimethyoxyethane and 1% tert butyl alcohol. Vapor was generated from aerosolized liquid. The rat strain was not specified. Rats were observed daily for toxic signs. Hematological examinations were given prior to exposure and after 1 and 4 weeks. At the study termination, the rats were sacrificed for gross and microscopic exams. No mortality or clinical signs of toxicity were observed during the study. No effects on body weight, hematology parameters, organ weights, and gross and microscopic pathology were observed. Chronic murine pneumonia varying from minimal to severe was noted in all rats. The lesions did not differ between treated and control rats.

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
INTERMEDIATE EXPOSURE								
				Cardio	380			
				Hemato	380			
				Hepatic	380			
				Renal	380			
				Bd Wt	140		380 (body weight gain reduced 51%)	

Calculations: 754 mg/m3 x 24.45 x 1/133.4 = 140 ppm; 2059 = 380 ppm.

Comments: Beagle dogs exposed to 92% pure 1,1,1-TCE. Test animals compared to 34 controls. No effect on hematologic values including leukocytes, hemoglobin, and hematocrit. No gross or histologic effects attributable to exposure. Body weight gain reduced 51% at 380 ppm.

177 Dog LSE 2NS (Beagle)	6 wk 5 d/wk 8 hr/d	0, 2210	BW GN HP BC	Resp	2210			Prendergast et al. 1967
				Cardio	2210			
				Hemato	2210			
				Hepatic	2210			
				Renal	2210			
				Bd Wt		2210 (body weight gain reduced >12%)		

Calculations: 12060 mg/m3 x 24.45 x 1/133.4 = 2210 ppm.

Comments: Beagle dogs exposed to 92% pure 1,1,1-TCE. Test animals compared to 34 controls from the 90-day study. No effect on hematologic values including leukocytes, hemoglobin, and hematocrit. No gross or histologic effects attributable to exposure. Reduced body weight gain (>12%), and actual loss of body weight (1.8%), in test animals.

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
INTERMEDIATE EXPOSURE								
199 Gerbil LSE 4-8M,4-8F (Mongolian)	3 mo 24 hr/d	0, 70	OW BI		70	(decreased DNA content in some brain areas)		Karlsson et al. 1987
Comments: Mongolian gerbils exposed to 95% pure 1,1,1-TCE. Three month TCE exposure followed by four month solvent-free period. No effect on brain weight or total protein concentration in any brain region (data not shown). Looked for effect on cell density in different parts of brain (DNA concentration analyzed as a measure of cell content). DNA concentration significantly reduced in posterior cerebellar hemisphere, anterior cerebellar vermis, and hippocampus (but not frontal cerebral cortex, sensory-motor cerebral cortex, occipital cerebral cortex, anterior cerebellar hemispheres, posterior cerebellar vermis, or brain stem). Lasting decrease in DNA concentration in 3 brain areas, indicating decreased cell density in these areas. This effect may be explained by loss of cells, which could be due to cell death or inhibition of non-neuronal cell acquisition.								
250 Gerbil LSE 4M,4F (Mongolian)	3 mo 24 hr/d	0, 70, 210, 1000	BI		70[c]		210 (increased GFA protein indicating astrogliosis)	Rosengren et al. 1985
Comments: Mongolian gerbils exposed to commercial cleaning grade 1,1,1-TCE (95% pure). 3 month exposure followed by 4 month solvent-free period. 3 month exposure chosen because it was sufficient to induce astroglial cell reactions in gerbil brain in experiments with other chemicals. Solvent-free period added to get information on lasting or permanent changes. 4 months was sufficient to repair transient astroglial cell reactions in previous experiments. Determined levels of the astroglial proteins S-100 and glial fibrillary acid protein (GFA) in the frontal cerebral cortex, sensorimotor cerebral cortex, and occipital cerebral cortex of the brain. Increased GFA protein in sensorimotor cerebral cortex at 210 and 1000 ppm (measured on both "per net weight of brain" and "per protein" bases). No effect on S-100 (except slight, but significant decrease in frontal cortex at 210 ppm on "per net weight" basis and increase in occipital cortex at 210 ppm on "per protein" basis; the significance of these changes is unclear since there was no effect at 1000 ppm in either case). No effect on protein concentration (except slight, but significant decrease in occipital cortex at 210 ppm; again significance unclear since no effect at 1000 ppm). Absolute brain weight was reduced at 1000 ppm (relative weight was not reported). Decreased brain weight could be due to atrophy of brain, but might just be due to dehydration. GFA protein is suitable marker to demonstrate formation of astroglial fibrils in response to brain injury (GFA is main protein subunit of astroglial filaments). Increased GFA in this study indicates astrogliosis. Demonstration of astrogliosis is considered strong evidence for CNS abnormality. S-100 found in both protoplasmic and fibrillary astrocytes and is suitable marker for astroglial cell increase in response to brain injury. Lack of effect on S-100 may be due to shift from protoplasmic to fibrillary astrocytes in response to TCE. Mechanism of TCE neurotoxicity unknown, but effects on brain membranes probable. Results indicate pronounced change in gerbil brain indicative of astrogliosis in cerebral sensorimotor complex. This change lasting or irreversible. Authors feel TCE should not be considered harmless.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
INTERMEDIATE EXPOSURE								
367 Rat 28M,28F (CDF)	90 d 5 d/wk 6 hr/d	0, 150, 500, 1000, 2000	BW GN HP BC CS BI OR UR		2000			Calhoun et al. 1981
Comments: Male and female CDF rats (Fischer 344 derived) were exposed to 1,1,1-TCE for 90 days, 5 days/week, 6 hours/day. Rats were evaluated for body weight, clinical signs of toxicity, clinical chemistry, hematological profile, urinalysis, and gross organ lesions. Gross and histological examination of the testes, prostate, epididymides, uterus, ovaries, oviducts, and cervix of the control and 2000 ppm groups revealed no lesions attributable to 1,1,1-TCE exposure.								
408 Rat 10M,10F (NS)	30 d 5 d/wk 7 hr/d	0, 1000	BW OW GN HP BC CS		1000			Dow Chemical Company 1969
Comments: 1,1,1-TCE contained 3% dimethyoxyethane and 1% tert butyl alcohol. Vapor was generated from aerosolized liquid. The rat strain was not specified. Rats were observed daily for toxic signs. At the study termination, the rats were sacrificed for gross and microscopic exams. No mortality or clinical signs of toxicity were observed during the study. Chronic murine pneumonia varying from minimal to severe was noted in all rats. There were no gross or histological alterations in the reproductive organs attributed to exposure to 1,1,1-TCE.								
266 Rat 20M (SPF-Wistar II)	14 wk 5 d/wk 8 hr/d	0, 204	OW GN HP		204 M			Eben and Kimmerle 1974
Comments: SPF-Wistar II rat used. No effect on testes weight or histopathology (4 test, 4 control).								
17 Rat 20M,20F (NS)	6 mo 5 d/wk 7 hr/d	0, 500	BW		500 M			Torkelson et al. 1958
Comments: Rats exposed to Chlorothene (94-97% 1,1,1-TCE). Concentration checked repeatedly, and was always within 10% of stated value. No effect on testes weight in males. Females not examined for reproductive effects.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
CHRONIC EXPOSURE								
706 Human 28NS	10 yr occup	NS	CS OR					Kelafant et al. 1994
Comments: Exposure occurred over a period of 10 years. The dermal route also contributed to the total exposure. Average age was 42 years. Sporadic exposure to other solvents had also occurred and many workers had direct or incidental exposure to asbestos and silica. Tests for hepatic function were unremarkable in all 28 cases; the same for results from electrocardiograms. Chest X-rays and pulmonary function tests revealed changes consistent with exposure to asbestos and silica.								
272 Human LSE 5-68B	up to 6 yr (occup)	<15, 15-49, 50-99, 100-149, 150-249	BC CS	Cardio	150			Kramer et al. 1978
				Hemato	150			
				Hepatic	150			
				Renal	150			
Comments: Matched-pair epidemiology study using two textile plants in same town. Workers in one plant were exposed to chlorothene NU (96% 1,1,1-TCE); those in the other plant were not. No difference in health exam responses. No effect on quantitative health measures, including blood pressure, heart rate, ECG, SGOT, SGPT, bilirubin, LDH, GGT, alkaline phosphatase, WBC, RBC, hemoglobin, hematocrit, and BUN. No deaths attributable to TCE over the 6 years of operation. No clinical pattern or other evidence of adverse effects in this study.								
510 Human 1M	NS	NS	OR					McLeod et al. 1987
Comments: This is a case report of a 14 year old boy who was suspected to have been sniffing 1,1,1-TCE over an undetermined period of time. He underwent anesthetization with halothane (among other drugs) for a tonsilectomy and experienced prolonged but transient complications, apparently due to anesthetization. Runs of ventricular tachycardias began during maintenence of his anesthesia with nitrous oxide, oxygen, and halthane during surgery. Complex arrythmias continued after a normal recovery from surgery, and dizzy spells and blackouts persisted for about 3 months after release from the hospital. The boy was suspected to have been sniffing throughout this period. Treatment with amiodarone after about 3 months eliminated the symptoms, and the boy was asymptomatic about 3 months after initiation of that treatment.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
CHRONIC EXPOSURE								
511 Human 1M	5 yr 5 d/wk 5 hr/d occup	NS	HP OR					McLeod et al. 1987
377 Rat 96M,96F (Sprague-Dawley)	12 mo 5 d/wk 6 hr/d	0, 875, 1750	BW OW GN HP BC CS BI OR UR	Resp	1750			Quast et al. 1978
				Cardio	1750			
				Gastro	1750			
				Hemato	1750			
				Musc/skel	1750			
				Hepatic	1750			
				Renal	1750			
				Dermal	1750			

Comments: This is a case report of a 54 year old man who had been occupationally exposed by inhalation to 1,1,1-TCE for about 5 hours per working day, over about 5 years. The air concentration in the workplace was not reported. Progressive cardiac complications ensued after anesthesia with halthane for repair of an inguinal hernia. Over the exposure period, the man became increasingly breathless, and was diagnosed with various respiratory ailmenst. At the end of the period of exposure, he was admitted to a hospital with congestive heart failure and atrial fibrillation. He was stabilized and remained stable on digitoxin for 6 years, at which time he underwent surgery for hernia. Over the following 5 months he became increasingly breathless. His left atrium and ventricle had enlarged since a routine checkup 4 years previously. Biopsy revealed severely hypertrophied myocardium, and evidence of healing myocarditis, but no evidence of viruses was present. Four and then again 7 months later he was readmitted with cardiac failure. The report does not provide further details of his fate, but he was being assessed for heart transplant. sp?

Comments: Male and female Sprague-Dawley rats were exposed to 1,1,1-TCE for 12 months and observed for their lifetimes (up to 31 months). The exposure control group contained 96 rats of each sex. Toxicological analysis included mortality, bone marrow cytogenetics, hematology, clinical chemistry, body and organ weight, gross and histologic examination of all major organs and tissues, urinalysis, and liver and kidney function tests. No lesions attributable to 1,1,1-TCE exposure were found after gross and histologic examination of all major organs and tissues except the liver. A slight decrease in hepatocyte size and hepatic glycogen content was observed in female rats exposed to 1750 ppm (not considered adverse).

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Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Oral

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE								
Death								
758 Rat LSE 4-6M (Sprague-Dawley)	Once (GO)	0; 500; 1,000; 2,000; 4,000 mg/kg	CS EA LE		4000 M			Bruckner et al. 2001

Descriptions: Groups of male Sprague-Dawley rats (4-6 per group) were administered 1,1,1-trichloroethane in a single oral gavage (in corn oil) dose of 0; 500; 1,000; 2,000; or 4,000 mg/kg and killed 24 hours later to assess potential adverse liver effects by liver weight and gross pathological examination, and measurements of serum liver enzyme levels and liver cytochrome P450 activity.

Results: There were no 1,1,1-trichloroethane-induced deaths prior to 24-hour sacrifice. There were no signs of adverse liver effects at any dose level. The authors indicated that CNS depression occurred, but did not state the dose level(s) at which this effect was noted.

778 Rat LSE 15-20M (Sprague-Dawley)	11 d d 1-5, 8-11 1x/d (GO)	0; 500; 5000; 10,000	BH BW CS GN HP LE		500 M		5000 M (3/15 died)	Bruckner et al. 2001

Descriptions: Groups of male Sprague-Dawley rats (number per group unspecified) were administered 1,1,1-trichloroethane by oral gavage (in corn oil), once per day on days 1-5 and 8-11 at doses of 0; 500; 5,000; or 10,000 mg/kg/day. Groups of up to 5 animals per dose level were sacrificed 1, 5, and 12 days following the initiation of treatment for evaluation of clinical chemistry and liver histopathology.

Results: The high doses resulted in numerous fatalities. Five of 10 high-dose that were not sacrificed after day 1 died by the third day of dosing. Only 1 high-dose rat survived until terminal sacrifice. Three treatment-related deaths were reported in the 5,000 mg/kg/day group, 2 of which occurred within 24 hours after the initiation of treatment. After each dosing, members of the 5,000 and 10,000 mg/kg/day groups exhibited 20-30 minutes of hyperexticability, followed by a protracted period of narcosis. No adverse effects were seen in rats of the 500 mg/kg/day group. The high-dose rats lost body weight during the the treatment period; the lone surviving high-dose rat exhibited a terminal body weight that was 47% lower than the control mean. Mean terminal body weight in the mid-dose group was 14% lower than controls. Clinical chemistry and liver histopathology did not reveal indications of 1,1,1-trichloroethane-induced liver injury.

713 Rat LSE 5M, 5F (Sprague-Dawley)	once (GO)	8000, 16000, 32000	LE				17148 M (LD50) 12996 F (LD50)	Kinkead and Wolfe 1992

Comments: 1,1,1-TCE (unspecified purity) was disolved in corn oil. Survivors were observed for 14 days following dosing. Mortality in males with the low, mid, and high dose was 0, 2, and 5, respectively. Mortality in females was 0, 4, and 5, respectively. No further information was provided.

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE								
				Bd Wt	1650			

Comments: 1,1,1-TCE was given in liquid paraffin vehicle. No effect on relative liver weight or the activities of liver enzymes (NADPH2-cytochrome-c reductase, aminopyrine demethylase, NADH2-cytochrome-c reductase, glucose-6-phosphatase, lactate dehydrogenase, glutamate dehydrogenase, glucose-6-phosphate dehydrogenase, and 6-phosphogluconate dehydrogenase) were observed. Liver microsomal and cell-sap proteins were increased. No effect on body weight was observed. Changes not considered adverse.

Subscript

77 Rat LSE 3-5M (Sprague-Dawley)	once (GO)	NS	BC	Hepatic		1330 M (ED50 for increased SGOT)		Tyson et al. 1983

Calculations: 10 mmol/kg x 133.4 mg/mmol = 1330 mg/kg.

Comments: 1,1,1-TCE was given in corn oil to fasted Sprague-Dawley rats. Effect on SGOT greater at 6 hr than at 24 hr. ED50 calculated at 6 hr. SGPT levels not affected.

78 Rat LSE 5-6M (Wistar)	1 d (GO)	0, 1370	BI	Hepatic	1370 M			Vainio et al. 1976

Calculations: 10.3 mmol/kg x 133.4 mg/mmol = 1370 mg/kg.

Comments: 1,1,1-TCE was given in olive oil to Wistar rats. Activity of cytochrome P-450 was reduced to half of control level. Activity of epoxide hydratase was also reduced. Activities of NADPH-cytochrome-c reductase, 3,4-benzpyrene hydroxylase, p-nitroanisole O-demethylase and UDP glucuronosyltransferase were unaffected. Changes were not considered adverse.

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
INTERMEDIATE EXPOSURE								
772 Rat 5M (F344/N)	1x/d 21 d (GO)	0, 83, 165	BH BW CS HP OW UR					NTP 1996 1,1,1-trichloroethane

Descriptions: NTP (1996) investigated renal and hepatic endpoints in a short-term study in which groups of 5 male F344/N rats were administered 1,1,1-trichloroethane (purity 100%) by gavage in corn oil at doses of 0, 0.62 or 1.24 mmol/kg-day (0, 83 or 165 mg/kg-day) for 21 days. Evaluations included survival, body weight gain, clinical signs, urinalysis (creatinine, glucose, total protein, AST, GGT, N-acetyl- -D-glucosaminidase, volume, specific gravity), organ weights (liver, right kidney, right testis) and limited histological assessment (liver, right kidney, gross lesions). The clinical and tissue pathology evaluations were limited in scope and centered on renal endpoints because this study was part of an investigation of structure-activity relationships involved in the induction of hyaline droplet nephropathy by halogenated ethanes.

Results: One rat in the 165 mg/kg-day group died on the second day of the study; the cause of death was not discussed. Otherwise, no clinical signs of toxicity were noted and body weights remained similar to controls throughout the study. Urinalysis revealed large, statistically significant increases in mean urinary protein (indicative of renal dysfunction, and possibly, tissue damage) and AST (indicative of renal tissue damage) in the survivors in the 165 mg/kg-day group. However, no histopathological lesions were found in the livers or kidneys of treated rats, including renal hyaline droplet nephropathy, tubule regeneration, or granular casts. Relative liver weight was significantly increased by 11% in the 165 mg/kg-day rats, and although not statistically significant, absolute liver weight was also 9% higher than controls in this group. There were no statistically significant changes in kidney or testis weight. NTP considered the urinalysis results to be highly suggestive of renal injury at 165 mg/kg-day, but also noted the lack of supporting histopathology data. The low n of 4 individuals in the 165 mg/kg-day group and the large standard errors for protein and AST concentrations in this group suggest that the increases in the corresponding means could be due to high levels in a single individual, and therefore, may not be related to treatment. Because of these questions about the urinalysis results and the lack of supporting histopathology data, it is not clear whether the observed urine changes indicate an adverse renal effect or whether any renal damage that did occur was related to treatment. Therefore, NOAEL/LOAEL values were not assigned.

the the

98 Mouse LSE 5M,5F (B6C3F1)	6 wk 5 d/wk (GO)	1000, 1780, 3160, 5620, 10000	CS				10000 (8/10 died)	NCI 1977

Comments: 95% pure 1,1,1-TCE was administered in corn oil to B6C3F1 mice. No mortality at 5620 mg/kg/day was observed, but 4/5 males and 4/5 females died at 10,000 mg/kg/day doses.

Systemic

783 Rat LSE 15-20M (Sprague-Dawley)	13 wk 5 d/wk 1 x/d 1x/d (GO)	0; 500; 2,500; 5,000	BH BW CS GN HP LE	Hepatic	500 M	2500 M (induction of serum liver enzymes)		Bruckner et al. 2001

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
INTERMEDIATE EXPOSURE								
				Bd Wt	2400 M	4800 M (10% decreased final body weight)		

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Descriptions: A thirteen-week feeding study was conducted in rats and mice (NTP, 2000). Groups of 10 male and 10 female F344/N rats, 6-7 weeks old at the start of the study, were fed diets containing 0 (untreated feed), 0 (placebo microcapsules), 5000, 10,000, 20,000, 40,000, or 80,000 ppm of microencapsulated 1,1,1-trichloroethane (>99% pure) 7 days/week for 13 weeks. Average daily doses calculated by the researchers were 290, 600, 1200, 2400, and 4800 mg/kg in male rats; and 310, 650, 1250, 2500, and 5000 mg/kg in female rats. Clinical signs and body weight were recorded weekly. Feed consumption was recorded every 3-4 days. Urine was collected for analysis and measurement of 1,1,1-trichloroethane metabolites from 5 randomly selected male rats in the vehicle control, 5000, 20,000 and 80,000 ppm groups on days 28 and 84. Blood for hematology and clinical chemistry determinations was collected from all rats at the end of the study, and from satellite groups of 10 male and 10 female rats (exposed to the same concentrations as the main study groups) on days 3 and 23. Vaginal cytology (over 12 days prior to sacrifice) and sperm motility (at necropsy) evaluations were performed on all main study rats and mice in the vehicle control, 20,000, 40,000, and 80,000 ppm groups at the end of the study. All animals in the main study were necropsied; organs and tissues were examined for gross lesions, and the heart, lungs, thymus, liver, right kidney, and right testis were weighed. Rats and mice in the untreated control, vehicle control, and 80,000 ppm groups in the main study received complete histopathological examinations. Rats in 5000, 10,000, 20,000 and 40,000 ppm main study groups were examined for renal histopathology only.

Too lengthy / needs trimming

Results: All rats survived to study termination and no clinical signs of toxicity were observed. Body weight gain over the course of the study was significantly reduced in the 80,000 ppm male rats in comparison to both the untreated and vehicle controls. Final body weight was 10% less than vehicle controls (statistically significant), but only 4% less than untreated controls (not significant). In the 80,000 ppm females, body weight gain and final body weight were lower than vehicle and untreated controls, but only the difference in final body weight versus vehicle controls (4.2 %) was statistically significant. Body weight changes in lower dose groups were unremarkable. Feed consumption was similar to controls in all groups. Hematology analyses revealed minimal increases in red blood cell count, hemoglobin, and hematocrit in male and female rats at 10,000 ppm and above. NTP considered these changes to indicate a minimal hemoconcentration effect likely due to physiological processes unrelated to 1,1,1-trichloroethane exposure. No toxicologically meaningful changes were found in clinical chemistry or urine analyses. Absolute and relative liver weights were significantly reduced by about 15% and 11%, respectively, in comparison to both untreated and vehicle controls in female rats treated with 80,000 ppm. In male rats treated with 80,000 ppm, absolute liver weight was significantly reduced by about 13% compared with vehicle controls, but did not differ from untreated controls, and relative liver weight was unaffected. Male rats treated with 20,000 ppm or above of 1,1,1-trichloroethane showed renal lesions characteristic of 2u-globulin nephropathy, as indicated by significant, dose-related increases in incidence and/or severity of renal tubule hyaline degeneration, cast formation, and regeneration, and chronic interstitial inflammation of the kidney. Assays for the presence of 2u-globulin were not conducted. No lesions in other tissues were observed in the males, and no lesions in any tissue were observed in the female rats. Treatment with 1,1,1-trichloroethane had no effect on vaginal cytology parameters in female rats. In males, epididymal spermatozoal concentration was significantly reduced by about 10% in the 80,000 ppm group compared with vehicle controls (untreated controls not tested), but no other associated changes were found. Renal changes associated with 2u-globulin nephropathy in male rats are specific to this sex and species, and are not considered to be predictive for effects in humans. Therefore, this study identified a LOAEL of 80,000 ppm (4800 mg/kg-day in males and 5000 mg/kg-day in females) and NOAEL of 40,000 ppm (2400 mg/kg-day in males and 2500 mg/kg-day in females), based on reduced body and liver weights in males and females and reduced epididymal spermatozoal concentration in males. ?

Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Oral

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
INTERMEDIATE EXPOSURE								
788 Mouse LSE 10 (B6C3F1)	Continuous 13 wk (F)	M: 0, 850, 1770, 3500, 7370, 15,000; 0, 1340, 2820, 5600, 11,125, 22,900	BH BW CS FI GN HE HP LE OW UR	Bd Wt	[b] 1770 M 2820 F	[c] 3500 M (>10% decreased terminal body weight, >20% depressed body weight gain) 5600 F (>10% decreased terminal body weight)		NTP 2000 ?

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Descriptions: Groups of male and female B6C3F1 mice (10 per group) were administered microencapsulated 1,1,1-trichloroethane in the diet at concentrations of 0, 5,000; 10,000; 20,000; 40,000; or 80,000 ppm, 7 days per week for 13 weeks. Untreated control groups of 10 males and 10 females were included in the study. Average doses of 1,1,1-trichloroethane calculated by the researchers 850, 1,770, 3,500, 7,370, and 15,000 mg/kg/day in male mice; and 1,340, 2,820, 5,600, 11,125, and 22,900 mg/kg/day in female mice. Clinical signs and body weights were recorded weekly. Food consumption was determined every 3-4 days. Vaginal cytology and sperm motility evaluations were performed on all mice in the vehicle control and 3 highest dose groups of mice. At necropsy, all mice were subjected to gross pathological examinations, and the heart, lungs, thymus, liver, right kidney, and right testis were weighed. Mice in untreated and vehicle control and high-dose groups were subjected to complete histopathologic examinations.

Results: There were no exposure-related deaths. Food consumption was slightly increased in 1,1,1-trichloroethane-treated groups, relative to untreated and vehicle controls. However, the final mean body weight of all groups of 1,1,1-trichloroethane-treated male mice was significantly lower (9, 9, 12, 10, and 15% lower in the 5,000-, 10,000-, 20,000-, 40,000-, and 80,000-ppm male groups, respectively) than that of the untreated controls. In the same order, Mean body weight gain in all treatment groups was also significantly less than that of the untreated controls (12, 16, 23, 22, and 33% ~~lower in 5,000-, 10,000-, 20,000-, 40,000-, and 80,000-ppm groups~~, respectively). There were no indications of treatment-related clinical or histopathological effects. According to ATSDR policy, a treatment-related decrease in body weight of 10% or more and a 20% or greater decrease in body weight gain (relative to controls) may be considered to represent an adverse effect.

Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Oral

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
INTERMEDIATE EXPOSURE								
Reproductive								
230 Rat LSE 36M,36F (Sprague-Dawley)	70 d ad libitum (W)	0, M: 0.27, 0.79, 2.39 F(premating): 0.31, 0.99, 2.96 F(gestation): 0.35, 1.16, 3.50 F(postnatal): 0.60, 1.99, 5.92	BW FI WI GN CS FX MX DX		2.96 F			NTP 1988a; George et al. 1989

Comments: 97% pure 1,1,1-TCE containing 1,4-dioxane was given to rats in drinking water at 3, 10, and 30 ppm using Tween 80 as emulsifying agent. Doses were calculated by the investigators based on body weight changes and water consumption data. Exposure began 2 weeks prior to mating and continued through day 21 of lactation. Test were rats compared to both untreated and Tween 80/p-dioxane controls. No mortality or clinical signs of toxicity during premating or mating. Slight concentration-dependent decrease in water consumption, indicative of mild taste aversion. During gestation, there was no mortality, no clinical sign of toxicity, and no effect on body weight, food consumption, or water intake. There was a small, but significant decrease in maternal body weight gain at high dose. There was no effect on the number of implantation sites/female, length of gestation, or maternal body weight during lactation.

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Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Oral

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
INTERMEDIATE EXPOSURE								
774 Rat LSE 10 (F344/N)	Continuous 13 wk (F)	M: 0, 290, 600, 1200, 2400, 4800 mg/kg/day; F: 0, 310, 650, 1250, 2500, 5000 mg/kg/day	BH BW CS FI GN HE HP LE OW UR		2400 M	4800 M (10% reduction in epididymal spermatozoal concentration)		NTP 2000

Descriptions: A thirteen-week feeding study was conducted in rats and mice (NTP, 2000). Groups of 10 male and 10 female F344/N rats, 6-7 weeks old at the start of the study, were fed diets containing 0 (untreated feed), 0 (placebo microcapsules), 5000, 10,000, 20,000, 40,000, or 80,000 ppm of microencapsulated 1,1,1-trichloroethane (>99% pure) 7 days/week for 13 weeks. Average daily doses calculated by the researchers were 290, 600, 1200, 2400, and 4800 mg/kg in male rats; and 310, 650, 1250, 2500, and 5000 mg/kg in female rats. Clinical signs and body weight were recorded weekly. Feed consumption was recorded every 3-4 days. Urine was collected for analysis and measurement of 1,1,1-trichloroethane metabolites from 5 randomly selected male rats in the vehicle control, 5000, 20,000 and 80,000 ppm groups on days 28 and 84. Blood for hematology and clinical chemistry determinations was collected from all rats at the end of the study, and from satellite groups of 10 male and 10 female rats (exposed to the same concentrations as the main study groups) on days 3 and 23. Vaginal cytology (over 12 days prior to sacrifice) and sperm motility (at necropsy) evaluations were performed on all main study rats and mice in the vehicle control, 20,000, 40,000, and 80,000 ppm groups at the end of the study. All animals in the main study were necropsied; organs and tissues were examined for gross lesions, and the heart, lungs, thymus, liver, right kidney, and right testis were weighed. Rats and mice in the untreated control, vehicle control, and 80,000 ppm groups in the main study received complete histopathological examinations. Rats in 5,000, 10,000, 20,000 and 40,000 ppm main study groups were examined for renal histopathology only.

Results: All rats survived to study termination and no clinical signs of toxicity were observed. Body weight gain over the course of the study was significantly reduced in the 80,000 ppm male rats in comparison to both the untreated and vehicle controls. Final body weight was 10% less than vehicle controls (statistically significant), but only 4% less than untreated controls (not significant). In the 80,000 ppm females, body weight gain and final body weight were lower than vehicle and untreated controls, but only the difference in final body weight versus vehicle controls (4.2 %) was statistically significant. Body weight changes in lower dose groups were unremarkable. Feed consumption was similar to controls in all groups. Hematology analyses revealed minimal increases in red blood cell count, hemoglobin, and hematocrit in male and female rats at 10,000 ppm and above. NTP considered these changes to indicate a minimal hemoconcentration effect likely due to physiological processes unrelated to 1,1,1-trichloroethane exposure. No toxicologically meaningful changes were found in clinical chemistry or urine analyses. Absolute and relative liver weights were significantly reduced by about 15% and 11%, respectively, in comparison to both untreated and vehicle controls in female rats treated with 80,000 ppm. In male rats treated with 80,000 ppm, absolute liver weight was significantly reduced by about 13% compared with vehicle controls, but did not differ from untreated controls, and relative liver weight was unaffected. Male rats treated with 20,000 ppm or above of 1,1,1-trichloroethane showed renal lesions characteristic of 2u-globulin nephropathy, as indicated by significant, dose-related increases in incidence and/or severity of renal tubule hyaline degeneration, cast formation, and regeneration, and chronic interstitial inflammation of the kidney. Assays for the presence of 2u-globulin were not conducted. No lesions in other tissues were observed in the males, and no lesions in any tissue were observed in the female rats. Treatment with 1,1,1-trichloroethane had no effect on vaginal cytology parameters in female rats. In males, epididymal spermatozoal concentration was significantly reduced by about 10% in the 80,000 ppm group compared with vehicle controls (untreated controls not tested), but no other associated changes were found. Renal changes associated with 2u-globulin nephropathy in male rats are specific to this sex and species, and are not considered to be predictive for effects in humans. Therefore, this study identified a LOAEL of 80,000 ppm (4800 mg/kg-day in males and 5000 mg/kg-day in females) and NOAEL of 40,000 ppm (2400 mg/kg-day in males and 2500 mg/kg-day in females), based on reduced body and liver weights in males and females and reduced epididymal spermatozoal concentration in males.

cut it short and merge

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
INTERMEDIATE EXPOSURE								
79 Mouse LSE 10M,30F (Swiss ICR)	25 wk ad libitum (W)	0, 100, 300, 1000	BW WI GN CS FX MX DX TG		1000			Lane et al. 1982

Comments: 97% pure 1,1,1-TCE containing p-dioxane was added to water of ICR Swiss mice in a multigeneration reproductive study. F0's were exposed for 5 weeks before first mating and continued 25 weeks; F1's were exposed for 11 weeks before first mating and continued for 24 weeks. No effects in either F0 or F1: no effect on fluid consumption, body weight, mortality, reproductive performance (number pregnant/number mated, the number with live litters/number pregnant), litter size, pup body weight, or pup survival (day 0 to day 4, day 4 to day 21). Authors conclude no evidence for reproductive toxicity.

787 Mouse LSE 10 (B6C3F1)	Continuous 13 wk (F)	M: 0, 850, 1770, 3500, 7370, 15,000; 0, 1340, 2820, 5600, 11,125, 22,900	BH BW CS FI GN HE HP LE OW UR		c 15000 M 22900 F			NTP 2000

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Descriptions: Groups of male and female B6C3F1 mice (10 per group) were administered microencapsulated 1,1,1-trichloroethane in the diet at concentrations of 0, 5,000; 10,000; 20,000; 40,000; or 80,000 ppm, 7 days per week for 13 weeks. Untreated control groups of 10 males and 10 females were included in the study. Average doses of 1,1,1-trichloroethane calculated by the researchers 850, 1,770, 3,500, 7,370, and 15,000 mg/kg/day in male mice; and 1,340, 2,820, 5,600, 11,125, and 22,900 mg/kg/day in female mice. Clinical signs and body weights were recorded weekly. Food consumption was determined every 3-4 days. Vaginal cytology and sperm motility evaluations were performed on all mice in the vehicle control and 3 highest dose groups of mice. At necropsy, all mice were subjected to gross pathological examinations, and the heart, lungs, thymus, liver, right kidney, and right testis were weighed. Mice in untreated and vehicle control and high-dose groups were subjected to complete histopathologic examinations.

Results: There were no exposure-related deaths. Food consumption was slightly increased in 1,1,1-trichloroethane-treated groups, relative to untreated and vehicle controls. However, the final mean body weight of all groups of 1,1,1-trichloroethane-treated male mice was significantly lower (9, 9, 12, 10, and 15% lower in the 5,000-, 10,000-, 20,000-, 40,000-, and 80,000-ppm male groups, respectively) than that of the untreated controls. Mean body weight gain in all treatment groups was also significantly less than that of the untreated controls (12, 16, 23, 22, and 33% lower in 5,000-, 10,000-, 20,000-, 40,000-, and 80,000-ppm groups, respectively). There were no indications of treatment-related clinical or histopathological effects. According to ATSDR policy, a treatment-related decrease in body weight of 10% or more and a 20% or greater decrease in body weight gain (relative to controls) may be considered to represent an adverse effect.

In the same order

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
INTERMEDIATE EXPOSURE								
Developmental								
82 Rat 6F (CD)	from before gestation thru lactation (W)	0, 1.4	BW OW DX TG				1.4 F (cardio anomalies)	Dapson et al. 1984; Hutcheon et al. 1985

Calculations: 10 mg/L x 0.049 L/day x 1/0.35 kg = 1.4 mg/kg/day.

Comments: 97% 1,1,1-TCE containing 1,4-dioxane was given to CD rats at 10 ppm in drinking water using Tween 80 emulsifier starting before gestation and continuing throughout lactation. Pups examined on postnatal days 21-23. No effect on pup body weight or heart weight was observed. Cardiovascular anomalies (persistent ductus arteriosis and atrial hypoplasia) in over 30% of pups of treated rats. Serum concentration of 1,1,1-TCE was 30 mg/mL.

750 Rat LSE 25F (Fischer- 344	Gd 6-21 Ld 1-10 (GO)	0, 75, 250, 750	BW CS DX MX GN HP FX		750			Dow Chemical 1993; Maurissen et al. 1994

Should be cut short

Comments: Groups of pregnant rats were gavaged with 1,1,1-TCE (99.9% pure) in corn oil from gestation day 6 through lactation day 10. ~~The purpose of the study was~~ to evaluate the neurobehavioral effects of 1,1,1-TCE on the offspring. Twenty litters/dose were used, and on postnatal day 4, litters were culled to 8 pups (4/sex). Endpoints examined included body weight (dams and pups), physical maturation landmarks (pinna detachment, incisor eruption, eye opening, testes descent and vaginal opening), motor activity (days 13, 17, 21, 44, and 59), functional observation battery (days 45 and 60), and brain measurements and neuropathology (days 28 and 62; pups only). Learning, task performance and short-term memory were tested at about 2-3 months of age. No lethality or clinical signs of toxicity were observed in adult females as a result of treatment with 1,1,1-TCE. The number of runts was increased in the 250 and 750 mg/kg/day groups, but the Fischer Exact Test revealed no statistical significance. Observation of the pups revealed no treatment-related effects. Analyses of maturational landmarks did not show any significant treatment-related effects. Body weight of the dams was not affected by 1,1,1-TCE during gestation or lactation. There was no effect on number of pups born alive, born dead, or litter size. Pups body weight were significantly reduced at the 75 and 750 mg/kg/day dose level, but not at 250 mg/kg/day. The authors questioned the biological significance of this effects given the lack of effects on maturational landmarks and the power of the statistical test to detect small differences. Results from the functional observation battery (hand-held and open field monitoring, and grip performance)(10 pups/sex/dose) were unremarkable. Analyses of auditory brainstem responses (days 22 and 61; 10/sex/dose) showed a slightly smaller response in the 75 mg/kg/day group on day 22, however, since the other groups showed no difference relative to controls, this effect was considered unlikely to be associated with exposure to 1,1,1-TCE. Motor activity (assessed in a cage by a computer) was not influenced by treatment with 1,1,1-TCE. Results from delayed matching-to-position tests showed that exposure to 1,1,1-TCE had no effects on short-term memory and did not impair learning or performance. No compound-related gross or microscopic alterations of the central and peripheral nervous system, skeletal muscle, and eyes were observed at necropsy of control and high-dose groups (3/sex/dose). Brain measurements (width, length, weight, 10/sex dose) were not affected by treatment with 1,1,1-TCE. Results from gross pathology examination of 20 dams/dose were unremarkable.

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
INTERMEDIATE EXPOSURE								
220 Rat LSE 37M,37F (Sprague-Dawley)	40 d ad libitum (W)	0, M: 0.26, 0.64, 2.0 F(premating): 0.30, 0.79, 2.0 F(gestation): 0.34, 0.84, 2.4	BW OW FI WI CS FX MX DX TG		2.4 F			NTP 1988b

Comments: 99% pure 1,1,1-TCE containing 1,4-dioxane was given to rats in drinking water at 3, 10, and 30 ppm using Tween 80 as emulsifying agent. Doses were calculated by the investigators based on body weight and water consumption data. Exposure began 2 weeks prior to mating and continued through day 20 of gestation. Test rats were compared to both untreated and Tween 80/p-dioxane controls. Premating and mating (male and female): no significant adverse effect on body weight, food intake, or water intake; no death; no clinical signs that were not also seen in controls. Gestation (F only): no effect on maternal body weight or maternal liver weight; significant dose-related increase in gravid uterine weight; no effect on maternal food or water consumption; no clinical signs that were not also seen in controls. Fetotoxicity: no adverse effect on the number corporea lutea/female, number of implantation sites/female, percent preimplantation loss, percent dead fetuses/litter, percent litters with dead fetuses, percent resorptions/litter, percent nonlive implants/litter, percent adversely affected implants/litter, percent litters with resorptions, nonlive implants, adversely affected implants, number of live fetuses/litter, percent male fetuses/litter, average fetal body weight/litter. Teratogenicity: no increase in malformations in fetuses on gestation day 20 (no effect on percent fetuses malformed/litter, percent litters with malformed fetuses, or type or incidence of external, visceral, or skeletal malformations). No cardiac abnormalities observed (looked for atrial hypoplasia, which was reported by Dapson et al. 1984). All normal fetuses on gestation day 20 have patent ductus arteriosis so efforts were focused on other cardiac malformations. Authors conclude no significant toxicity in parental generation and no developmental toxicity in this study.

Reduce IC Leaf

80 Mouse LSE 10M,30F (Swiss ICR)	25 wk ad libitum (W)	0, 100, 300, 1000	DX FX TG MX BW WI GN CS		1000			Lane et al. 1982

Comments: pure 1,1,1-TCE containing p-dioxane was added to water of ICR Swiss mice in a modified multigeneration reproductive study. F0's were exposed for 5 weeks before first mating and continued 25 weeks; F1's were exposed for 11 weeks before first mating and continued for 24 weeks. Teratology screen: no effect on number mated/number with live fetuses (fecundity), number implants/female, number of resorptions/female, number live fetuses/female, ratio of dead/live fetuses, percent female with dead fetuses, or sex ratio of fetuses. No increase in incidence of visceral or skeletal malformations. Dominant lethal screen: no effect on the number of pregnant female/number available (fertility), number of implants/females, number resorptions/females, number of live fetuses/females, percent females with dead fetuses, number of live treated fetuses/number live untreated fetuses (frequency of dominant lethal factors). Ratio of dead/live fetuses was increased, but not dose-related and higher in vehicle control than test groups anyway. Authors conclude no evidence for developmental toxicity.

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
CHRONIC EXPOSURE								
451 Human NS	2 yr environ (W)	NS	DX					Wrensch et al. 1990a,b

Comments: Epidemiology study conducted to investigate relationship between drinking water contamination with 1,1,1-TCE and adverse pregnancy outcomes in San Jose, California. Follow-up to Dean et al. 1989. Original study broadened to include a second exposed census tract (but without any cluster reported) and a second control tract, and a comparison of post-exposure period pregnancies (1982-1985) in addition to exposure period pregnancies (1980-1981). Verifying the finding of the earlier study, the odds ratio for spontaneous abortion was significantly increased (to 3.5) in the original exposed area during 1980-1981. during 1982-1985, the odds ratio declined to 1.0 in this tract. The odds ratio was not significantly elevated in the "new" exposed area during 1980-1981 or 1982-1985. Multivariate adjustment for potential confounders had little effect on these results. The odds ratio for malformations was significantly elevated to 4.3 in the original exposed area during 1980-1981, and declined to 1.2 during the post-exposure period. There was no elevated prevalence of malformations in the "new" exposed area, however. Prevalence of low birth weight babies was similar in all 4 study areas during the exposure and post-exposure periods. Hydrogeologic exposure assessment showed that the "new" exposed area consistently received a greater percentage of water from the contaminated well than the original exposed area. Analysis of individual pregnancy outcomes in the 2 exposed areas during 1981 in relation to hydrogeologic exposure assessment showed that 1,1,1-TCE exposure during the first month of pregnancy was slightly higher in the 104 successful pregnancies (1052 ppb) than the 20 spontaneous abortions (824 ppb) and that the 6 births with malformations had significantly lower average exposure during the first trimester (354 ppb) than live births without malformations (1111 ppb). These results suggest that the cluster of adverse pregnancy outcomes in the original exposed area, although real, was not produced by consumption of water from the contaminated well.

Cancer

221 Human 93-945NS	In home drinking water supply (W)	.000003	CS		3.0E-6			Isacson et al. 1985

Comments: Epidemiology study comparing people exposed to measurable concentrations of 1,1,1-TCE in drinking water to controls. 0.1 µg/L, which produces a dose of 0.000003 mg/kg/day, was detection limit. No difference was found between people exposed to at least 0.000003 mg/kg/day (i.e. those living in towns with at least 0.1 µg/L in water supply) and people exposed to less than 0.000003 mg/kg/day in incidence of bladder, colon, lung, breast, prostate, or rectum cancer. Other cancers not looked at, and only people 355 years old included.

235 Rat 40M,40F (Sprague-Dawley)	104 wk 4-5 d/wk (GO)	0, 500	GN HP			500 (Increased leukemia)		Maltoni et al. 1986

Comments: Technical grade (95% pure) 1,1,1-TCE containing 4% 1,4-dioxane was given to Sprague-Dawley rats in olive oil for 104 weeks. Test rats were compared to 50 male and 50 female vehicle controls. Animals observed for 141 weeks (allowed to live until natural death). There was an increased incidence of leukemias, especially immunoblastic lymphosarcomas of the lung. There were 13 leukemias in treated rats vs 4 in controls. These included 7 immunoblastic lymphosarcomas in treated rats (5 in males, 2 in females-all in lungs) versus 1 in controls. Size and design of experiment do not allow definite conclusions about 1,1,1-TCE carcinogenicity.

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Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Oral

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
CHRONIC EXPOSURE								
104 Rat 50M,50F (Osborne-Mendel)	78 wk 5 d/wk (GO)	0, 750, 1500	GN HP		1500			NCI 1977
Comments: Technical grade (95% pure) 1,1,1-TCE in corn oil was given to Osborne-Mendel rats. Experiment included 20 male and 20 female untreated controls, but no vehicle controls. CCl4 was used as positive control. Animals were observed for 110 weeks. All animals were necropsied. No effect on incidence or type of neoplasms. This study not adequate because early mortality may have affected incidence of late-appearing tumors.								
111 Mouse 50M,50F (B6C3F1)	78 wk 5 d/wk (GO)	0, 2807, 5615	GN HP		5615			NCI 1977
Comments: Technical grade (95% pure) 1,1,1-TCE in corn oil was given to B6C3F1 mice. Experiment included 20 male and 20 female untreated controls, but no vehicle controls. Doses reported represent time-weighted averages. CCl4 was used as positive control. Animals were observed for 90 weeks. All animals were necropsied. No effect on incidence or type of neoplasms. This study was not adequate because early mortality may have affected incidence of late-appearing tumors.								

Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Dermal

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
Death								
502 Human 1M	<2 hr	NS	GN BC					Jones and Winter 1983
Comments: This is a case report of a 20 year old man who died after less than 2 hours of inhalation exposure and probable concurrent dermal exposure to 1,1,1-TCE while using the solvent as a degreasing agent. The concentration in the room was apparently not measured, although the room was noted to be "fume-filled," and solvent-induced dermal changes were observed on all exposed skin. After an inquest, death was reported to have been caused by respiratory suppression that was secondary to central nervous system depression.								
83 Gn Pig 20NS (NS)	1 d	0, 7360	CS					Wahlberg and Boman 1979
Calculations: 2 mL x 1339 mg/mL x 1/0.364 kg = 7360 mg/kg.								
Comments: Single application to clipped back in 3.1 cm2 glass disk, which was then covered to prevent inhalation or ingestion. Disk stayed on 5-7 days (long enough to allow all 1,1,1-TCE to be absorbed). No mortality was observed during 35 day observation period.								
237 Rabbit 5M (New Zealand)	1 d 24 hr/d neat	2680	CS					Kinkead and Leahy 1987
Calculations: 2 mL/kg x 1339 mg/mL = 2680 mg/kg.								
Comments: 1,1,1-TCE 96.4% pure (measured). New Zealand White rabbits used. Undiluted 1,1,1-TCE applied to clipped back and covered with gauze, clear plastic wrap, and tape. Removed after 24 hours. No mortality was observed during 14 day observation period.								
9 Rabbit LSE 8NS (NS)	1 d 24 hr/d	3980, 15800	CS			15800 mg/kg/day	(under 50% mortality)	Torkelson et al. 1958
Comments: Both impure (94-97% 1,1,1-TCE with 2.4-3.0% dioxane) and pure 1,1,1-TCE tested. Materials were applied for 24 hours under a cuff. High dose killed less than half the test animals. Authors conclude low toxicity by this route.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
INTERMEDIATE EXPOSURE								
Immuno/ Lymphoret								
11 Rabbit LSE 4M (NS)	90 d 5 d/wk	0, 15, 50, 100, 200, 500	OW GN HP		500 M mg/kg/day			Torkelson et al. 1958
Comments:	1,1,1-TCE (2.4-3.0% dioxane) was applied directly to shaven skin without cover. Skin abraded in 2 of the 4 rabbits in each group. Rabbits kept under fume hood with head protruding to prevent inhalation. One from each group killed after 30 and 90 days for internal examination. Remainder autopsied after another 30 days. No adverse effects on spleen found by internal examination.							
Neurological								
448 Human 3F	1-5 mo occup	NS	HP CS OR					Liss 1988; Howse et al. 1989
Comments:	Case report of 3 women who developed peripheral neuropathy after frequent prolonged dermal contact with 1,1,1-TCE at their place of work. Nerve conduction studies and sural nerve biopsies were performed. The patients initially complained of numbness in the limbs and were found to have alterations in nerve activity. Sural nerve biopsies performed in 2 patients 3-4 years later revealed chronic ongoing neuropathy (axonopathy and myelinpathy). The neuropathy was primarily a distal sensory peripheral neuropathy. It was unusual in that the hands were more affected than the feet.							
12 Rabbit LSE 4M (NS)	90 d 5 d/wk	0, 15, 50, 100, 200, 500	OW GN HP		500 F mg/kg/day			Torkelson et al. 1958
	if it is same exp., why the write up is different?							
Comments:	Inhibited 1,1,1-TCE (2.4-3.0% dioxane) was applied directly to shaven skin without cover. Skin abraded in 2 of the 4 rabbits in each group. Rabbits kept under fume hood with head protruding to prevent inhalation. One from each group killed after 30 and 90 days for internal examination Remainder autopsied after another 30 days. No adverse effects on the brain found by internal examination.							
Reproductive								
13 Rabbit LSE 4M (NS)	90 d 5 d/wk	0, 15, 50, 100, 200, 500	OW GN HP		500 M mg/kg/day			Torkelson et al. 1958
Comments:	Inhibited 1,1,1-TCE (2.4-3.0% dioxane) was applied directly to shaven skin without cover. Skin abraded in 2 of the 4 rabbits in each group. Rabbits kept under fume hood with head protruding to prevent inhalation. One from each group killed after 30 and 90 days for internal examination. Remainder autopsied after another 30 days. No adverse effects on the testes were found by internal examination.							

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Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Other

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE								
Death								
437 Rat 5-10M (Sprague-Dawley)	once (IP)	NS	CS BI				5088 M (LD50)	Klaassen and Plaa 1969
Comments: Sprague-Dawley rats were injected with analytical grade 1,1,1-TCE in corn oil. LD50 was based on 24 hours observation period. 95% CI: 4419-5624 mg/kg.								
132 Mouse NSF	1 d (IP)	NS	BC CS				4700 F (LD50)	Gehring 1968
Calculations: 25.2 mol/kg x 133.4 mg/mol = 4700 mg/kg. ? check the calculations, it should be 3362								
Comments: LD50-mice were observed for 24 hours; 95% CI: 4323-5123 mg/kg.								
120 Mouse NS (NS)	1 d (IP)	NS	CS				3700 (LD50)	Gradiski et al. 1978
Comments: No details were provided.								
399 Mouse NS (NS)	once (IP)	NS	CS				4980 (LD50-20 °C) 3636 (LD50-30 °C)	Horiguchi et al. 1991
Comments: The LD50 decreased as the ambient temperature increased. Few experimental details were provided. Confidence limits were not calculated.								

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Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Other

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE								
85 Gn Pig 10 NS (NS)	1 d (IP)	0, 7172	CS				7172 (8/10 died)	Wahlberg and Boman 1976
Comments: 8/10 died within 2 hrs. 2 survived. 0/10 controls died.								
441 Dog 5B (NS)	once (IP)	NS	HP BC CS OR				4136 (LD50)	Klassen and Plaa 1967
Comments: Mongrel dogs of both sexes were injected with 1,1,1-TCE in corn oil. LD50 and ED50 values were calculated using the "up and down" method so each determination involved only 5 dogs. The confidence limits were not calculated. LD50 was based on mortality within 24 hours of injection.								
Systemic								
398 Rat 5F (Sprague-Dawley)	3 wk 5 d/wk (IP)	0, 500	UR	Renal	500 F			Bernard et al. 1989
Comments: Sprague-Dawley rats were ~~used.~~ with Analytical grade 1,1,1-TCE ~~was~~ administered in olive oil (2.5 mL/kg). Controls received olive oil only. They were monitored for urinary excretion of N-acetyl-B-D-glucosaminidase, B2-microglobulin and albumin. No significant difference from controls.								
397 Rat 6M (Sprague-Dawley)	once (IP)	0, 1330	HP BC	Hepatic	1330 M			Charbonneau et al. 1991
Comments: Sprague-Dawley rats were ~~used.~~ with 1,1,1-TCE (97% pure) ~~was~~ administered in corn oil (4 mL/kg injection volume), with or without concurrent administration of other haloalkanes. The injection was preceded 18 hours earlier by gavage dose of corn oil (10 mL/kg) or acetone (10.2 mmol/kg) in corn oil. 1,1,1-TCE alone had no effect on SGPT or liver histopathology. Acetone pretreatment had no effect on these results. Binary mixtures of 1,1,1-TCE with other haloalkanes produced less than additive liver toxicity, with or without acetone pretreatment.								

Summary Table for Toxicity Studies for Exposure to 1,1,1-Trichloroethane - Other

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE								
438 Rat 5-10M (Sprague-Dawley)	once (IP)	NS	CS BI	Hepatic	3749 M			Klaassen and Plaa 1969
Comments: Sprague-Dawley rats were injected with analytical grade 1,1,1-TCE in corn oil. LD50 was based on 24 hours observation period. 95% CI: 4419-5624 mg/kg. At 3749 mg/kg, no effect on liver triglyceride levels, glucose 6-phosphatase activity, or lipid peroxide levels were observed. In vitro, lipid peroxidation was significantly increased at a dose of 10 mL, and decreased at higher doses (50-200 mL).								
395 Rat 5-6M (Sprague-Dawley)	once (IP)	0, 2000	BW OW BC	Hepatic	2000 M			Stacey 1989
				Renal	2000 M			
Comments: Sprague-Dawley rats were used. The purity of 1,1,1-TCE was not specified. Controls were injected with 0.6 mg/kg corn oil. 1,1,1-TCE had no effect on relative liver weight or serum GPT or SDH. 1,1,1-TCE had no effect on serum urea levels. Simultaneous injection with other haloalkanes did result in toxic effects. A similar pattern of interactive toxicity was found using suspensions of rat hepatocytes in vitro.								
400 Rat 6M (Sprague-Dawley)	once (IP)	0, 2135	OW BC	Hepatic		2135 M (decreased relative liver weight, increased SGOT)		Stacey 1989
				Renal	2135 M			
Comments: Sprague-Dawley rats were ~~used. The purity of 1,1,1-TCE was not reported.~~ with 1,1,1-TCE ~~was~~ administered in corn oil; control received 0.6 mg/kg corn oil i.p. Relative liver weight was slightly, but significantly, reduced by 1,1,1-TCE, and SGOT was significantly increased. SGPT and LDH were unaffected. Co-treatment with other haloalkanes produced some positive interaction. A similar pattern of interaction toxicity was found using rat hepatocytes in vitro. 1,1,1-TCE had no effect on serum urea levels, even when co-administered with other haloalkanes. (purity not reported)								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE								
281 Rat 10M (Osborne-Mendel)	1 d (IP)	0, 1320	BW OW HP	Hepatic	1320 M			Story et al. 1986
				Bd Wt	1320 M			

Calculations: 9.9 mmol/kg x 133.42 = 1320 mg/kg.

Comments: 97% pure 1,1,1-TCE (3% dioxane) was administered to Osborne-Mendel rats. Rat liver foci assay for cancer initiation potential (gamma-glutamyltranspeptidase (GGT) used as marker). Enzyme-altered foci are potentially capable of developing into hepatocellular carcinoma. Phenobarbital (PB) in diet for 7 weeks starting 1 week after i.p. injection of 1,1,1-TCE [which was 24 hours after partial hepatectomies (2/3 of liver cut off)]. Negative control - corn oil alone. Positive control - diethylnitrosamine (DEN) - 30 mg/kg. GGT foci was quantified using light microscope. No effect on the number of GGT(+) foci with/without ~~phenobarbital~~ PB promotion. No effect on body weight or relative liver weight. Data not shown. No evidence for cancer initiation by 1,1,1-TCE.

133 Mouse NSF (NS)	1 d (IP)	NS	BC	Hepatic		2908 F (ED50 for increased SGOT)		Gehring 1968

Comments: ED50 for increased SGOT:blood taken at 24 hours after injection; 95% CI: 2642-3202 mg/kg. LD50/ED50 potency ratio = 1.62.

440 Mouse 10M (Swiss)	once (IP)	NS	HP BC CS OR UR	Hepatic		3336 M (increased SGPT [ED50])		Klassen and Plaa 1966
				Renal	4937 M			

Comments: Swiss-Webster mice were injected with analytical grade 1,1,1-TCE in corn oil. The LD50 was based on a 24 hour observation period. Delayed deaths occurred, but were not included in the LD50 calculation. 95% CI on LD50: 4136-5870 mg/kg. Liver effects indicated by elevated SGPT (ED50 = 3336 mg/kg) and increased BSP retention (ED50 = 3602 mg/kg) at near-lethal doses. Histopathological examination revealed enlargement of hepatocytes with cellular infiltration and vacuolation at near-ED50 doses, as well as slight necrosis of near-LD50 doses. No effects on kidney (PSP excretion, urinalysis, histopathology), even at lethal doses were observed. Pre-treatment with and ataxia-inducing dose of ethanol (5 g/kg/day by gavage in water, 1 or 3 days prior to 1,1,1-TCE injection) significantly increased the effect on the liver (BSP retention, but not SGPT), but not the kidney (PSP excretion).

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE								
436 Mouse 10M (Swiss)	once (IP)	3348, 6695	HP CS UR	Renal		3348 M (tubular swelling)		Plaa and Larson 1965
Comments: Swiss mice were injected with 1,1,1-TCE in corn oil. 7 high-dose and 1 low-dose mouse died within 24 hours of injection. 1/9 surviving low-dose mice had proteinuria. All low-dose mice examined histologically had renal tubular swelling.								
447 Mouse 5-10M (Princeton)	once (SB)	5203, 10407, 13342, 16010	GN HP CS OR	Hepatic	5203 M	11207 M (ED50 for increased phentobarbital narcosis)		Plaa et al. 1958
Comments: Princeton mice were injected with commercial grade 1,1,1-TCE in peanut oil. 10-day LD50 = 16,010 mg/kg (95% CI: 12,675-21,347 mg/kg). Liver function was tested by determination of sleeping time following i.p. injection of 45 mg/kg sodium phenobarbital. ED50 for this effect was 11,207 mg/kg for 1,1,1-TCE. Varying degrees of central necrosis were found in the livers of mice injected with high doses of 1,1,1-TCE. BSP retention was affected only at 16,010 mg/kg.								
445 Mouse NSM (CF-1)	once (IP)	NS	BC CS	Hepatic		3214 M (increased SGPT [ED50])		Preistly and Plaa 1976
Comments: CF-1 Swiss-derived mice were injected with 1,1,1-TCE in corn oil. 24 hour LD50 = 4017 mg/kg (95% CI: 3481-4553 mg/kg). ED50 for elevation of SGPT = 3214 mg/kg (95% CI: 3080-3348 mg/kg). Serum alkaline phosphatase was not increased by 1,1,1-TCE. Concurrent injection of nicotine HCL (5 mg/kg in saline) significantly increased the lethality of 1,1,1-TCE (LD50 reduced to 3214 mg/kg), but had no effect on SGPT levels produced by 1,1,1-TCE.								
186 Mouse 5F (NS)	1 d	400	BI	Hepatic	400 F			Takahara 1986
Calculations: 3 mmol/kg x 133.42 mg/mmol = 400 mg/kg.								
Comments: The author claims very mild decrease in liver ATP and increase in liver triglycerides. No statistical information provided, but does not appear to be any real effect. No controls, just pre-exposure values.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE								
434 Mouse 10M (Swiss)	once (IP)	1339, 2678, 3348	BC	Hepatic	2678 M	3348 M (increased SGPT)		Trarger and Plaa 1974
Comments: Swiss-Webster mice were injected with 1,1,1-TCE in corn oil. SGPT was elevated in the high dose group. Pre-treatment with acetone or isopropyl alcohol by gavage 18 hours before 1,1,1-TCE injection had no effect on SGPT levels produced by 1,1,1-TCE.								
116 Dog 5NS (NS)	1 d 1 hr/d (IT)	0, 200, 500, 700, 1000, 1500, 2000	BC	Hemato	200	500 (decreased leukocytes)		Hobara et al. 1983a
Comments: At 700 ppm for 1 hour, leukocytes decreased at start of exposure and continued down to 69% decrease at end of exposure. Recovered back to 35% decrease within 1 hour. Neutrophils also declined markedly and lymphocytes increased rapidly. This peaked at end of exposure and returned to normal afterwards. No effect on red blood cell, hematocrit, or thrombocyte counts. Leukocyte count decrease was dose related from 200 to 700 ppm. Effect may be due to trapping of neutrophils from peripheral blood in other tissues and may be only temporary.								
118 Dog 5NS (NS)	1 d 4 hr/d (IT)	700	BC	Hemato		700 (decreased leukocytes)		Hobara et al. 1983a
Comments: No effect on red blood cell, hematocrit, or thrombocyte counts. Leukocyte count decreased to minimum at 90 minutes (25% of control) then began to increase (reached 40% of control at 240 minutes.								
119 Dog 5NS (NS)	1 d (IV)	50	BC	Hemato		50 (decreased leukocytes)		Hobara et al. 1983a
Comments: Data was not shown, but no effect on erythrocytes, thrombocytes, hematocrit was observed. Leukocyte count decreased 61% at 30 minutes, then increased to 20% decrease at 120 minutes.								
442 Dog 5B (NS)	once (IP)	NS	HP BC CS OR	Hepatic		1147 (ED50 for increased SGPT)		Klassen and Plaa 1967

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
530 Human 1M,1F	once	NS	AB					Hall and Hine 1966
Results: The blood concentration of 1,1,1-TCE was 13 and 72 mg% in the man and woman, respectively.								
Comments: This is a report of 2 cases, one a 29 year old man and the other a 19 year old woman, who apparently inhaled a lethal concentration of 1,1,1-TCE. The fatal concentrations were not estimated, although the woman had been sniffing cleaning fluid for several days, and the man had died with a rag soaked in cleaning fluid over his mouth.								
339 Human 12M,3F	1 d 2-4 hr/d	13.2- 90.7	UM					Imbriani et al. 1988
Results: Subjects were exposed to 1,1,1-TCE at concentrations ranging from 72-495 mg/m3 for 2-4 hours. Samples of alveolar air and urine were analyzed for 1,1,1-TCE. The relative fractional uptake of 1,1,1-TCE decreases from 0.44 to 0.26 at rest and from 0.26 to 0.22 during light exercise. A linear relationship was seen between urinary concentration and time weighted average concentration, (r > 0.90). A linear relationship was also found between urinary concentration and amount of 1,1,1-TCE absorbed (r = 0.88). Dose in mg/m3 x 24.45/133.42(mw) = ppm.								
Comments: Urinary concentration of 1,1,1 TCE is an appropriate biological indicator for exposure.								
341 Human 60NS	1 d 4 hr (occup)	32.6	EX UM					Imbriani et al. 1988
Results: Urinary concentrations of 1,1,1-TCE were determined (before and after a workshift) in 60 workers in a refrigerator manufacturing plant. Personal monitors yielded estimates of exposure; the median value for TWA concentration was 178 mg/m3. A linear relationship was found between urinary concentration of 1,1,1-TCE and the TWA exposure concentration (r = 0.95). The urinary concentration corresponding to the TWA of the TLV was 860 æg/L and its 95% lower confidence limit (biological threshold) was 805 æg/L. Dose in mg/m3 x 24.45/133.42 = ppm.								
Comments: The authors proposed that urinary concentration is an appropriate method for determining exposure to 1,1,1-TCE.								
527 Human 1M	<2 hr	NS	AB DI					Jones and Winter 1983
Results: 1,1,1-TCE was detected in the blood, brain, and liver at 4.2 mg/100 mL, 123 mg/100 g, and an unreported concentrations, respectively.								
Comments: This is a case report of a 20 year old man who died after less than 2 hours of inhalation exposure and probable concurrent dermal exposure to 1,1,1-TCE while using the solvent as a degreasing agent. The concentration in the room was apparently not measured, although the room was noted to be "fume-filled," and solvent-induced chemical changes were observed on all exposed skin.								

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Summary Table for Toxicokinetic Studies for Exposure to 1,1,1-Trichloroethane - Inhalation

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
390 Human 48M	1 d 8 hr	26.3	EX UM					Kawai et al. 1991

Results: Exposure to 1,1,1-TCE was determined (with personal monitors) during an 8-hour workshift in 48 exposed male workers in a printing shop and 10 non-exposed male workers. The geometric mean of time-weighted average exposures for exposed workers was 26.3 ppm; the highest estimated exposure was 65 ppm. Urine was collected during exposure and at the end of the workshift and analyzed for metabolite concentrations (trichloroacetic acid and trichloroethanol). Statistically significant positive linear correlations were observed between time-weighted average exposure concentrations and urinary concentrations of trichloroacetic acid or trichloroethanol.

Comments: The results suggest that urinalysis for trichloroeacetic acid and trichloroethanol provides a means for monitoring occupational exposure to 1,1,1-TCE. Theoretical calculations indicated that less than 2% of absorbed 1,1,1-TCE was excreted as metabolites in urine.

529 Human 2M,2F	NS	NS	AB					King et al. 1985

Results: The blood of 2 and the lung tissue of 3 kids were examined for the presence of 1,1,1-TCE, and were found to be positive in each case. The blood concentration of 1 13 year old girl was quantified, and reported to be 2.0 mg/L 1,1,1-TCE.

Comments: This is a report of 4 cases of young adults (aged 13-18 years old) who died after intentionally sniffing TCF (liquid paper), which contains 1,1,1-TCE. The air concentration of the solvent was not estimated. TCF also contains trichloroethylene, among other constituents.

531 Human 3M	once	NS	AB					MacDougall et al. 1987

Results: Blood concentrations of 1,1,1-TCE in the 3 boys were 0.003, 0.2, and 7.4 æg/g blood.

Comments: This is a report of 3 fatal cases of inhalation of 1,1,1-TCE in a thinning fluid (Tipp-Ex) in boys of 13-15 years of age. The air concentrations of the solvent, and other solvents in the thinner were not reported.

312 Human 6M	1 d 4 hr/d	70, 142, 145	AB EX UM					Monster et al. 1979

Results: Average uptake was 192.5 mg at 70 ppm, 429.2 mg at 145 ppm and 537.5 mg at 142 ppm plus workload. Subjects were exposed to 70 ppm and 145 ppm at rest and to 142 ppm at rest combined with work load (2 x 30 min, 100 watt workload). Minute volume and concentration in exhaled air estimated uptake. 1,1,1-TCE, trichloroethanol (TCE) and trichloroacetic acid (TCA) were determined in blood, exhaled air and urine. During exposure, the lung clearance quickly decreased - 6.0 L/min initially to 1.91 L/min at 4 hours. The uptake increased 2.3 fold during work load and the minute volume increased about 3-fold. 60-80% of 1,1,1-TCE taken up was excreted unchanged by the lungs, while 70 hours after exposure, the amount of TCE and TCA in the urine represented approximately 2% and 0.5% of uptake, respectively.

Comments: Work load increased the rate of uptake of 1,1,1-TCE. Total uptake was more influenced by minute volume than by body weight or amount of adipose tissue. Most of the inhaled 1,1,1-TCE is excreted uncharged in exhaled air.

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
345 Human 5NS	once	NR	EX RM					Morgan et al. 1970
Results: Human blood:air and serum:air partition coefficients were determined to be 1.4 and 3.4 respectively. Measurements of radioactivity in exhaled breath for one hour following administration of a single held breath containing 5 mg of radiolabelled 1,1,1-TCE, showed that 44% of the administered dose was exhaled. Blood:air partition coefficients for a number of chlorinated methanes and ethanes were negatively correlated with measured activities exhaled following breath holding. Measurement of radioactivity in urine collected 1 hour following dose administration indicated that the rate of urinary excretion was less than 0.01% of administered dose per minute.								
Comments: The authors speculated that differences in blood:air partition coefficients influence absorption rates of chlorinated methanes and ethanes and that these differences may explain why these compounds have differing toxicities.								
313 Human NR	1 d	NR	AB EX					Morgan et al. 1972a,b
Results: Partition coefficients for 1,1,1-TCE were determined in olive oil/gas (139) and in serum/gas (7). When breath was held for 15-45 seconds after inhalation of 1,1,1-TCE, retention in the lungs was 80-90% as indicated by alveolar air monitoring. By 30 minutes after administration of single breaths, approximately 60-70% of the administered dose remained in the lungs. Data were not reported for exhalation periods longer than 30 minutes.								
Comments: 1,1,1-TCE was absorbed more rapidly and completely that tested fluorochlorohydrocarbons with lower lipid solubility. Doses administered and/or number of subjects were not reported.								
296 Human 6M	1 d 6hr/d	35, 350	AB EX UM					Nolan et al. 1984
Results: Urine blood and expired air samples were collected for up to 9 days after exposure. Disposition of inhaled 1,1,1 TCE: a) 350 ppm concentration: ~~91.97~~% 92.0 expired, 4.9% metabolized, 0.8% in body after 9 days: b) 35 ppm exposure: 91.3% expired, 6.0% metabolized and 0.6% in body after 9 days. The amount of TCE and TCA (two major metabolites) were determined in the urine. The total amounts of TCE and TCA excreted account for 77% of the predicted amount of metabolized 1,1,1 TCE. About 25% of the inhaled dose was absorbed during the 6 hour exposure.								
Comments: 1) Elimination of 1,1,1 TCE was triexponential with half-lives estimated at 44 min, 5.7 hr, and 53 hr for the initial, intermediate & terminal phases. Over 91% of the absorbed dose was excreted unchanged by the lungs, 5-6% was metabolized and excreted as TCA & TCE and less than 1% remained in the body after 9 days. Kinetics of 1,1,1 TCE are suggested to be first order.								
526 Human 1M	once	NS	AB DI					Northfield 1981
Results: Tissue concentrations were 27 mg/100 mL and 188 mg/100 g in blood and lung, respectively.								
Comments: A young man of 16 years died after apparently intentionally sniffing 1,1,1-TCE on the job, as evience by an unspecified skin "reaction" around his mouth. Fellow employees had found him in a "stuporose" condition on 2 previous occasions. The normal exposure concentration at his work station was reported to be 65 ppm, and 735 ppm with the ventilation system turned off.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
322 Rat 3M	1 d 2-6 hr/d	0.2, 1.0, 10, 210	AB					Gargas et al. 1986
Results: Fisher rats were used. Tissue and liquid air partition coefficients determined and incorporated into a physiological kinetic model. First-order pathway required for 1,1,1-TCE. Pyrazole abolished the first-order pathway.								
Comments: In vivo metabolic constants determined from gas-uptake data using models.								
308 Rat 6B	1 d 8 hr/d	0, 200	UM					Ikeda & Ohtsuji 1972
Results: Wistar rats were exposed for 8 hours and urine was collected for 48 hours. Urine was analyzed for total trichlorocompounds (TTC), trichloroacetic acid (TCA), and trichloroethanol (TCE). Comparison to trichloro and tetrachloro-derivatives of ethane and ethylene was done. 3.6 mg/kg TTC, 0.5 mg/kg TCA and 3.1 mg/kg TCE were collected after 48 hours.								
Comments: Very small amounts of metabolites were found in the urine compared with other solvents tested. This was consistent with vapor pressures of the solvents: 1,1,1-TCE has the highest vapor pressure and the lowest boiling point of the solvents tested and it was almost completely excreted in the expired air (very little in urine). Solvents with low vapor pressure were absorbed and excreted as metabolites in the urine. Concentration of 1,1,1-TCE or metabolites in the expired air were not determined.								
720 Rat 5M	6 hr	50, 100, 500	UM EX					Kaneko et al. 1994
Results: The results showed that pretreatment with ethanol increased the metabolism of 1,1,1-TCE at all concentrations tested. This was inferred by an increase in the urinary excretion of the metabolites trichloroacetic acid and trichloroethanol (main metabolite). Ethanol, however, did not influence the time course of disappearance of 1,1,1-TCE from blood. This is consistent with the fact that 1,1,1-TCE is eliminated mainly unchanged.								
Comments: Rats were maintained on a control diet or a diet containing 2 g ethanol/day/rat for up to three weeks. After this period, the rats were exposed under dynamic conditions to the test material, and the concentration of 1,1,1-TCE was determined in blood and metabolites analyzed in urine over several hours.								
323 Rat 7M	1 d 8 hr/d	350	UM					Koizumi et al. 1982
Results: Wistar rats were used. Urine collected during the 8 hours of exposure and during the following 16 hours. Total trichlorocompounds (TTC) trichloroacetic acid (TCA) and trichloroethanol (TRI-OH) were determined. The main metabolite of 1,1,1-TCE was TRI-OH (164.6 ñ= 42.9 æg/kg/hour during exposure and 77.7 ñ= 17.6 æg/kg 1 hour after exposure). Tetrachloroethylene suppressed the metabolism and excretion of 1,1,1-TCE.								
Comments: Metabolism of 1,1,1-TCE was suppressed by tetrachloroethylene by two possibilities: a) suppression of the oxidation of 1,1,1-TCE to TRI-OH. b) Both chemicals oxidized by hepatic microsomal mixed function oxidase system (MFOS), which may preferentially oxidize tetrachloroethylene if it is present.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
338 Rat NR M	5 d 6 hr/d	500	DI					Savolainen 1981
Results: Incorporation of 1,1,1-TCE into the perirenal fat was logarithmic. Coefficient of regression (R) = 0.99. Fat-stored molecules of 1,1,1-TCE were not mobilized during lapses in exposure. After 5 days of exposure, approximately 250 nmol/gm were incorporated into fat. The effect of accumulation when 1,1,1-TCE was administered in combination with other solvents was discussed.								
Comments: Incorporation of 1,1,1-TCE into adipose tissue was logarithmic. Number of animals per group was not reported.								
334 Rat 10M	4-5 d 6 hr/d	0, 500	DI EA					Savolainen et al. 1977
Results: The animals were exposed for 4 days or for 4 days plus 2, 3, 4, or 6 hours on the fifth day. After exposure for 4 days, 1,1,1-TCE was found primarily in the perirenal fat (16.9 nmol/gm). As the time of exposure on the fifth day increased, the concentration of 1,1,1-TCE steadily increased in the perirenal fat (peak value after 6 hours = 27.6 nmol/g) in the liver (peak value = 21.3 nmol/g), in the blood (peak value = 13.1 nmol/g), in the lungs (peak = 11.7 nmol/g) and in the brain (peak cerebrum = 15.6 nmol/g, peak cerebellum = 21.3 nmol/g). A decrease in liver microsomal cytochrome P-450 and RNA content in liver was seen on the 5th day of exposure.								
Comments: No effects on behavior were observed as a result of 1,1,1-TCE exposure. 1,1,1-TCE preferentially accumulated in the perirenal fat. Only two animals assessed per time point. Liver, lung and brain were the only organs examined for 1,1,1-TCE content.								
302 Rat 4M	1 d 6 hr/d	150, 1500	AB DI EX UM FM RM					Schumann et al. 1982a
Results: Fisher rats were used. [14C] 1,1,1-TCE was used. Elimination of [14C] 1,1,1-TCE was followed for 72 hours. >96% of the administered [14C] 1,1,1-TCE was excreted during the first 24 hours post-exposure. The major route of excretion was via unchanged solvent in the expired air (94% at 150 ppm, 98% at 1500 ppm). The remaining radioactivity was detected as metabolized 1,1,1-TCE as [14C] in expired air, and as non volatile radioactivity in the urine, feces, carcass and cage wash. Biotransformation of 1,1,1-TCE was shown to be a saturable, dose-dependent process. The 1,1,1-TCE distributed initially to the liver, kidneys & fat and was rapidly cleared so that by 24 hours post-exposure, <2% remained.								
Comments: 1,1,1-TCE shows little potential for significant bioaccumulation in rodents. Mice eliminated 1,1,1-TCE in expired air more rapidly than rats. Mice metabolized 2-3 times more 1,1,1-TCE on a body weight basis than rats. Only the liver, kidney & fat were analyzed for 1,1,1-TCE content.								
722 Rat NS	1 d 2 hr/d	1000	DI					Wilmer et al. 1993
Results: The results obtained were consistent with the model prediction that 1,1,1-TCE would be cleared from the brain faster than from adipose tissue due to the high level of vascular perfusion of the brain. No further details were provided in this abstract.								
Comments: Brain levels of 1,1,1-TCE were determined in Fischer 344 rats at various intervals (unspecified) during and after exposure to vapors of 1,1,1-TCE. These levels were compared to those predicted by a physiologically-based pharmacokinetic model.								

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^{14}C

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
327 Mouse NR	1 d 10 min/d	approx 20 µCi	DI					Danielsson et al. 1986

Results: C57BL mice were used. 14C-1,1,1-TCE was used. Total activity and non-volatile activity were assessed at 0, 30 min, 4 hr, 24 hr after exposure. Non-volatile implies 1,1,1-TCE was metabolized. Total activity in various organs at 0, 30 min, 4 hrs and 24 hrs were: 1) brain: 123 dpm/mg, 15 dpm/mg, 1.4 dpm/mg, 0.3 dpm/mg 2) lung: 114 dpm/mg, 17 dpm/mg, 6.6 dpm/mg, 2.0 dpm/mg. 3) liver: 143 dpm/mg, 39 dpm/mg, 13 dpm/mg, 5.3 dpm/mg. 4)kidney: 97 dpm/mg, 49 dpm/mg, 7.2 dpm/mg 1.4 dpm/mg. Very little 1,1,1-TCE was metabolized. 1,1,1-TCE crossed the placental barrier and resulted in low levels in the fetus (9.3 dpm/mg, 7.8 dpm/mg, 2.1 dpm/mg, 0.7 dpm/mg. At 0, 30 min, 4 hr, 24 hr) and placenta (14 dpm/mg, 12 dpm/mg, 2.6 dpm/mg and 0.9 dpm/mg at 0, 30 min, 4 hr & 24 hrs). 14C

Comments: Very little 1,1,1-TCE is metabolized. Any metabolism that does occur happens in the liver. The number of animals was not reported.

332 Mouse 3-10M	1 d 0.5-24 hr/d	10, 100, 1000, 5000, 10000	DI TM					Holmberg et al. 1977

Results: Albino mice were used. The distribution of 1,1,1-TCE in the blood, liver, kidney & brain at different concentrations and exposure times was determined. The concentration of 1,1,1-TCE in the blood, kidney and brain were generally of the same magnitude for a given exposure time. The liver concentrations were higher. There was a linear relationship between inspired air concentration and tissue concentration at fixed exposure times. A correlation was seen between blood and organ concentrations in animals exposed to different concentrations but not at one fixed concentration. A high concentration for a short exposure time resulted in 10 times higher organ concentration than a low concentration over a long exposure period. 196

Comments: First order pharmacokinetic model for both uptake and elimination. Post-exposure concentrations were linear in a semilog graph. A one-compartment pharmacokinetic model was in accordance with the data.

304 Mouse 4M	1 d 6hr/d	150, 1500	AB DI EX UM FM RM					Schumann et al. 1982a

Results: B6C3F1 mice were used. [14C] 1,1,1-TCE was used. Elimination of [14C] 1,1,1-TCE was followed for 24 hours. >96% of the administered dose was excreted during the first 24 hours post-exposure. The major route of excretion was via unchanged solvent in expired air (87% at 150 ppm, 97% at 1500 ppm). The remaining radioactivity was detected as metabolized. 1,1,1-TCE as [14CO2] in expired air, and as nonvolatile radioactivity in the urine, feces, carcass and cage wash. Biotransformation of 1,1,1-TCE was shown to be a saturable dose-dependent process. The 1,1,1-TCE distributed initially to the liver, kidney, and fat and was rapidly cleared so that by 24-hours post-exposure, <2% remained. 14C

Comments: 1,1,1-TCE shows little potential for significant bioaccumulation in rodents. Mice eliminated 1,1,1-TCE in expired air more rapidly than rats. Mice metabolized 2-3 times more 1,1,1-TCE on a body weight basis than rats. Limitations: only the liver, kidney and fat were analyzed for 1,1,1-TCE content. There were small numbers of animals per group.

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
394 Mouse 4F	1 d 1 hr	500	DI					Shimada et al. 1988
Results: Four pregnant dd mice were exposed to 1000 ppm 1,1,1-TCE for one hour. Measured concentrations of 1,1,1-TCE in maternal tissues were 50.48, 66.09, 26.19, 79.82, 373.95, and 48.22 æg/g fresh tissue or mL of blood for liver, kidneys, brain, blood, fat, and placenta, respectively; the concentration in fetal tissue was 18.75 æg/g fresh tissue.								
Comments: The results demonstrate that inhaled 1,1,1-TCE is distributed to the placenta and fetuses in pregnant mice at concentrations comparable with concentrations in other organs and tissues, except fat which appears to accumulate notably higher concentrations of the compound.								
333 Mouse NR F	1 d 1 hr/d	1000	DI TM					Takahara 1986a
Results: At 0, 30, 60 and 120 minutes post-exposure, blood samples were taken. At 120 minutes, the heart, lung, liver, kidney, spleen, brains, peritoneal, fat and other tissues were analyzed for 1,1,1-TCE content. The level of 1,1,1-TCE was greatest in the adipose tissue (1314.21 æg at 0 minutes - 353.32 æg at 120 minutes) followed by the liver (135.28 æg at 0 minutes - 15.74 æg at 120 minutes) and the kidney (18.44 at 0 minutes - 3.06 æg at 120 minutes). The 1,1,1-TCE was rapidly cleared from the tissue by two hours. Rapid clearance from the blood also occurred (95.11 æg at 0 minutes - 15.78 æg at 120 minutes). is it possible?								
Comments: 1,1,1-TCE is preferentially taken up by the adipose tissue, liver and kidneys and is rapidly cleared from these tissues after exposure ends. Biological half-life of 1,1,1-TCE was shorter than the half-life for 1,1,2-TCE.								
309 Dog 5NS	1 d 1 hr/d	700, 1500, 2000	RM					Hobara et al. 1982
Results: Cumulative uptake of 1,1,1-TCE by the lungs in one hour: 27.3 mg/kg at 700 ppm, 44.7 mg/kg at 1500 ppm, 71.2 mg/kg at 2000 ppm. Excretion rates of unchanged compound in exhaled air during the first hour after exposure ceased were estimated to be: 17.9 mg/kg for 700 ppm, 30.1 mg/kg for 1500 ppm and 48.7 mg/kg for 2000 ppm. The mean ratio of total absorption to total inspired air during one hour exposure was 14% at all exposure levels. A significant negative correlation was seen in arterial/venous blood concentration ratio and expired/inspired air concentration ratio during exposure, and a significant positive correlation was seen between expired air concentration and venous or arterial blood concentration in the post-exposure period.								
Comments: Most of the inspired 1,1,1-TCE (66-71%) is expired unchanged by the lungs within 1 hour after exposure.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
CHRONIC EXPOSURE								
329 Human 30B	NR	NR	DI TM					Alles et al. 1988
Results: Mean values of 1,1,1-TCE in human tissues were determined in 30 autopsy cases. The mean values were 3, 3, 2, 7, 5 æg/kg wet tissue in subcutaneous fat, kidney fat, liver, lung and muscle, respectively.								
Comments: 1,1,1-TCE was found in the tissue of all of the subjects examined. The subjects were selected without regard to age or sex, but the majority of subjects were men between 60 and 70 years old. Report is in German.								
299 Human 10-26M	5 yr 5.5 d/wk 8 hr/d	4, 25, 28, 53	UM					Seki et al. 1975
Results: The total trichloro compounds excreted in the urine were 2.0 mg/L at 4.3 ppm, 8.2 mg/L at 24.6 ppm and 13.9 mg/L at 53.4 ppm. The concentration of TCE was 1.2 mg/L at 4.3 ppm, 5.5 mg/L at 24.6 ppm and 9.9 mg/L at 53.4 ppm. The concentration of TCA was 0.6 mg/l at 4.3 ppm, 2.4 mg/l at 24.6 ppm and 3.6 mg/L at 53.4 ppm. Levels of urinary metabolites increased as the week progressed, but decreased when exposure ceased on the weekend.								
Comments: A linear relationship was seen between environmental vapor concentrations and total trichloro-compounds in urine. Increased levels of urinary metabolites towards the end of the work week, together with the biological half-life of 8.7 hrs, suggest there is storage of 1,1,1-TCE in the body after repeated exposure.								
303 Rat 4M	16 mo 5 d/wk 6 hr/d	1500	EX UM RM					Schumann et al. 1982b
Results: Fisher rats were used. On the last day of exposure, 14C-labeled 1,1,1-TCE was used. For comparison, a group of rats was concurrently exposed to chamber air and, after 16 months, received a single exposure to 14C-labeled 1,1,1-TCE. The animals were sacrificed immediately or 72 hours after exposure. The routes of excretion and tissue concentration of 14C-1,1,1-TCE were similar. The major route of excretion was unchanged, 1,1,1-TCE in expired air (97%). The remaining radioactivity was recovered as 14CO2 in expired air and as nonvolatile radioactivity in the urine, feces, carcass, and cage wash. 1,1,1-TCE accumulated in the fat, liver and kidney and was virtually gone from all organs by 72 hours.								
Comments: No alterations in the pharmacokinetics of 1,1,1-TCE occur with prior repeated exposure. Most of the 1,1,1-TCE is quickly excreted unchanged in expired air. Mice eliminated 1,1,1-TCE more rapidly in expired air and biotransformed about 5 times more 1,1,1-TCE on a body weight basis than rats. Young animals showed an increased body burden and a decreased rate of pulmonary elimination of 1,1,1-TCE compared with older animals.								

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Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
CHRONIC EXPOSURE								
305 Mouse 4M	16 mo 5 d/wk 6 hr/d	1500	EX UM RM					Schumann et al. 1982b

Results: B6C3F1 mice were used. On the last day of exposure, 14C-labeled 1,1,1-TCE was used. For comparison, a group of mice was concurrently exposed to chamber air and, after 16 months, received a single exposure to 14C-labelled 1,1,1-TCE. The animals were sacrificed immediately or 72 hours after exposure. The routes of excretion and tissue concentration of 14C-1,1,1-TCE were similar. The major route of excretion was unchanged 1,1,1-TCE in expired air (92-94%). The remaining radioactivity was recovered as 14CO2 in expired air and as nonvolatile radioactivity in the urine, feces, carcass and cage wash. 1,1,1-TCE accumulated in the fat, liver and kidney, and was virtually gone from all organs by 72 hours. 14C

Comments: No alterations in the pharmacokinetics of 1,1,1-TCE occur with prior repeated exposure. Most of the 1,1,1-TCE is quickly excreted unchanged in expired air. Mice eliminated 1,1,1-TCE more rapidly in expired air and biotransformed about 5 times more 1,1,1-TCE on a body weight basis than rats. Young animals showed an increased body burden and a decreased rate of pulmonary elimination of 1,1,1-TCE compared with older animals.

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Summary Table for Toxicokinetic Studies for Exposure to 1,1,1-Trichloroethane - Oral

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
337 Rat 6M	once (G)	14.2	DI					Reitz et al 1988
Results: Following gavage administration of [2-14C]-labeled 1,1,1-TCE in water to male rats; blood levels of 1,1,1-TCE reached peak levels of approximately 2.8 mg/L about 5 minutes after dose administration. Levels declined to about 0.2 mg/L by 2 hours after dosing.								
Comments: The results show that oral absorption is rapid. The levels of 1,1,1-TCE in blood after gavage administration correlated fairly well with a proposed pharmacokinetic model.								
321 Rat M	1 d 8 hr/d	116	UM RM TM					Reitz et al. 1988
Results: Male Fisher rats were given 8 hour free access to drinking water containing [2-14C]-labeled 1,1,1-TCE (average dose = 116 mg/kg). The elimination of 1,1,1-TCE was rapid in expired air, virtually all was eliminated by 30 hours post-exposure. The amount of 1,1,1 TCE metabolized was represented by the amount recovered in the urine and as CO2 expired by the lungs (8.19 µmol = approx 3% of ingested dose). Overall recovery of the administered dose in expired air, urine and selected tissues (56 hours post-administration) was 95.2 ñ 4.33%, thereby indicating that nearly complete oral absorption occurred.								
Comments: 1,1,1-TCE was rapidly and nearly completely absorbed from ingested drinking water and rapidly eliminated. A PBPK model predicted that 5.49 æmol of 1,1,1-TCE (approximately 2% of ingested 1,1,1-TCE) would be metabolized. This correlates well with the actual amount metabolized (8.19 æmol = approximately 3% of ingested dose).								
378 Rat 3-4M	once (GO)	0, 100, 300, 1000	AB DI EX UM FM RM					RTI 1987
Results: 1,1,1-TCE labeled with 14C was administered by gavage to rats and the absorption, distribution and excretion were monitored over a 24-hour period. 1,1,1-TCE was rapidly excreted in the expired air. More than 80% of the administered dose was excreted in 8 hours. After 24 hours, 97% of the administered dose had been excreted in expired air. Only 1% was recovered in urine and 0.5% in the feces. 1,1,1-TCE is widely distributed throughout the body with the greatest concentration in adipose tissue and a smaller concentration in skeletal muscle. Similar tissue distributions were observed at 1 and 24 hours. 1,1,1-TCE was rapidly absorbed and blood concentrations were closely correlated with expired air concentrations.								
Comments: 1,1,1-TCE is rapidly absorbed after oral administration and is rapidly excreted almost exclusively in expired air. Very little excretion occurs in the urine or feces. 1,1,1-TCE is distributed mainly to adipose tissue but only trace amounts remain in the body after 24 hours.								
389 Mouse 4F	once (G)	50, 250, 50	AB EX					Gargas 1990
Results: Immediately following oral dose administration, mice were placed in an exhaled breath chamber system. Air samples were removed at intervals for up to 6 hours following dosing and analyzed for 1,1,1-TCE concentrations. Concentrations rose within the first hour in the chamber (maxima were positively correlated with dosage level) and then fell at fairly constant rates. The chamber concentrations were analyzed using a physiologically based pharmacokinetic model in which the oral absorption rate constant was varied until agreement was achieved between simulated and experimental results (metabolism was assumed to be negligible); this analysis determined an oral absorption rate constant of 0.72 hour-1.								
Comments: The results demonstrate rapid oral absorption of 1,1,1-TCE in rats, but an estimate of the extent of oral absorption (i.e., fractional absorption) was not obtained.								

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Summary Table for Toxicokinetic Studies for Exposure to 1,1,1-Trichloroethane - Oral

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE								
379 Mouse 3F	once (GO)	0, 300, 1000, 3000	AB DI EX UM FM RM					RTI 1987

Results: 1,1,1-TCE labeled with 14C was administered by gavage in vegetable oil to mice and the absorption, distribution, and excretion were monitored over a 24 hour period. The bulk of the administered dose of 1,1,1-TCE was excreted in the expired air within 4 hours of dosing. More than 90% of the administered doses was recovered in expired air within 24 hours. Two hours after administration, the adipose tissue contained three times more 1,1,1-TCE than any other tissue. Skeletal muscle, stomach, and skin also contained appreciable levels of 1,1,1-TCE. Within 24 hours of dose administration, only trace amounts of 1,1,1-TCE remained in the body. 14C

Comments: In mice, 1,1,1-TCE is excreted primarily in expired air after oral administration. 1,1,1-TCE is widely distributed throughout the body but is in highest concentration in the adipose tissue, skeletal muscle, stomach, and skin. 1,1,1-TCE is rapidly cleared from the body since only trace amounts were found 24 hours after administration.

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Summary Table for Toxicokinetic Studies for Exposure to 1,1,1-Trichloroethane - Oral

Species/ No. & Sex/ Strain Ref. #	Exposure/ Duration/ Frequency (Specific Route)	Doses	Parameters Monitored	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
INTERMEDIATE EXPOSURE								
325 Rat NR	4 wk 5 d/wk (G)	750, 3000						Mitoma et al. 1985

Results: Osborne-Mendel rats were treated for 4 weeks with unlabeled 1,1,1-TCE, then to a single dose of [14C] 1,1,1-TCE. The animals were sacrificed 48 hours later. At 3000 mg/kg - metabolic disposition of 1,1,1-TCE: 85.13% expired air and 4.12% metabolized (0.87% CO2, 2.05% excreta, 1.2% carcass). The amount metabolized was 0.28 mmol/kg at 750 mg/kg and 0.91 mmol/kg at 3000 mg/kg. The hepatic protein-binding was 2.58 and 7.68 nmol/mg protein for 750 and 3000 mg/kg, respectively. 14C

Comments: Metabolic disposition was greater in mice (6% of dose at 4000 mg/kg) than in rats (4% of dose at 3000 mg/kg). The recovery of radiolabel in expired air, urine and metabolites in carcasses indicated that nearly complete absorption of the administered doses occurred. Hepatic protein binding was comparable in mice and rats.

326 Mouse NR	4 wk 5 d/wk (G)	1000, 4000	AB EX					Mitoma et al. 1985

Results: B6C3F1 mice were treated for 4 weeks with unlabeled 1,1,1-TCE, then to a single dose of [14C] 1,1,1-TCE. The animals were sacrificed after 48 hours. Metabolic disposition of 1,1,1-TCE at 4000 mg/kg: 92.94% expired air, 6.09% metabolized (2.01% CO2, 3.36% excreta, 0.72% carcass). The amount metabolized was 0.60 and 1.81 mmol/kg for 1000 and 4000 mg/kg, respectively. The hepatic protein binding was 1.99 and 7.42 nmol/mg protein for 1000 and 4000 mg/kg, respectively.

Comments: Metabolic was greater in mice (6% at 4000 mg/kg) than in rats (4% at 3000 mg/kg). Hepatic protein binding was comparable in rats and mice. metabolism ?

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α-trichloromethane. Its registered trade names are chloroethene NU® and Aerothene TT®. It is a colorless liquid with a sweet, sharp odor. 1,1,1-Trichloroethane dissolves slightly in water. The liquid evaporates quickly and becomes a vapor in the air. Most people begin to smell 1,1,1-trichloroethane in the air when levels reach 120 –500 parts of 1,1,1-trichloroethane per one million parts of air (ppm). If the chemical makes up 8–10.5% (80,000–105,000 ppm) of the air, 1,1,1-trichloroethane can burn easily when it comes in contact with a spark or flame. If the vapor burns at high temperatures such as those produced during welding operations, it can produce a poisonous gas known as phosgene. Because of its tendency to evaporate easily, the vapor form is most commonly found in the environment. 1,1,1-Trichloroethane also can be found in soil and water, particularly at hazardous waste sites.

this is confusing. Presumably, none is being made today.

1,1,1-Trichloroethane was used in commercial products, mostly to dissolve other chemicals. About 800 million pounds were produced in 1990, but less is being made today. No 1,1,1-trichloroethane is supposed to be manufactured domestically after January 1, 2002 in the United States because it affects the ozone layer. 1,1,1-Trichloroethane had many industrial and household uses. It was often used as a solvent to dissolve other substances, such as glues and paints. In industry, it was widely used to remove oil or grease from manufactured metal parts. In the home, it used to be an ingredient of products such as spot cleaners, glues, and aerosol sprays.

At least in the U.S.

You will find detailed information on the chemical properties of 1,1,1-trichloroethane in Chapter 4. Chapter 5 describes production data and the uses of 1,1,1-trichloroethane.

1.2 WHAT HAPPENS TO 1,1,1-TRICHLOROETHANE WHEN IT ENTERS THE ENVIRONMENT?

Most of the 1,1,1-trichloroethane released into the environment enters the air, where it lasts for about 6 years. Once in the air, it may travel to the upper part of the earth's atmosphere, which is called the stratosphere. There, sunlight breaks it down into other chemicals that may reduce the stratospheric ozone layer. This ozone layer blocks certain damaging ultraviolet rays of the sun

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they use different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for 1,1,1-trichloroethane include the following:

"Not produce"

The EPA sets regulations on the levels of 1,1,1-trichloroethane that are allowable in drinking water. The highest level of 1,1,1-trichloroethane allowed in drinking water is 0.2 ppm. The EPA has decided that the level of 1,1,1-trichloroethane in lakes and streams should not be more than 18 ppm. This level would prevent possible harmful health effects from drinking water and eating fish contaminated with 1,1,1-trichloroethane. Any releases or spills of 1,1,1-trichloroethane of 1,000 pounds or more must be reported to the National Response Center. 1,1,1-Trichloroethane levels in the workplace are regulated by OSHA. The workplace exposure limit for

an 8-hour workday, 40-hour workweek is 350 ppm in air. See Chapter 8 for more information on regulations and advisories regarding 1,1,1-trichloroethane.

may want to make a statement as to how this amount is estimated/determined.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles CD-ROM by calling the toll-free information and technical assistance number at 1-888-42ATSDR (1-888-422-8737), by e-mail at atsdric@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO 1,1,1-TRICHLOROETHANE IN THE UNITED STATES

1,1,1-Trichloroethane is a synthetic chemical. In 2003, the estimated capacity of the commercial production of 1,1,1-trichloroethane in the United States was 510 million pounds (SRI 2003). Under the Clean Air Act as amended in 1990, all production of 1,1,1-trichloroethane was scheduled to cease as of January 1, 2002 (EPA 2004m). It may be used for essential applications such as medical devices and aviation safety (for the testing of metal fatigue and corrosion of existing airplane engines and other parts susceptible to corrosion) until January 1, 2005. 1,1,1-Trichloroethane was predominantly used as a chemical intermediate in the manufacture of hydrochlorofluorocarbons (HCFCs). It was also commonly used in vapor degreasing and cold cleaning, adhesives, coatings and inks, textiles, and electronics (CMR 1995).

1,1,1-Trichloroethane was released to the environment during the course of its manufacture, formulation, and use. It was frequently detected in the atmosphere and in water. In 2001, environmental releases of 1,1,1-trichloroethane reported under the EPA Toxics Release Inventory (TRI) program were about 207 thousand pounds in air emissions, 27 pounds in water discharges, 5 pounds in underground injection discharges, and 169 pounds in releases to land (TRI01 2004).

these amts. seem small in view of the > 500 million lbs produced

Monitoring studies of the ambient air levels of 1,1,1-trichloroethane in urban areas have reported concentrations in the range of 0.1–1 ppb, while the concentrations in rural areas have been reported to be <0.1 ppb (Table 6-3). Representative data taken from five geographic areas located throughout the United States report indoor concentrations of 0.3–4.4 ppb ok and outdoor concentrations of 0.11–0.92 ppb ok (Pellizzari et al. 1986). A more recent EPA region V (Minnesota, Wisconsin, Michigan, Illinois, Indiana, and Ohio) National Human Exposure Assessment Survey (NHEXAS) detected a mean concentration of 1,1,1-trichloroethane to be 1.15 ppb ok in indoor air samples collected from residential areas from July 1995 to May 1997 (Bonanno et al. 2001).

Levels of 1,1,1-trichloroethane detected in water ways near sources of emissions such as industrial waste water, hazardous waste sites, and spill locations are usually <1 ppb. Drinking water from surface or

And the fact that most of it eventually goes into air.

groundwater sources contained 1,1,1-trichloroethane concentrations of 0.01–3.5 ppb (Table 6-2). Limited monitoring data are available for the presence of 1,1,1-trichloroethane in soil. 1,1,1-Trichloroethane is expected to rapidly volatilize from soil and to leach through soil.

Environmental exposures of humans to 1,1,1-trichloroethane have been correlated with levels of parent compound and 1,1,1-trichloroethane metabolites (trichloroethanol and trichloracetic acid) in expired air, blood, and urine (Hartwell et al. 1987a; Monster 1986; Wallace et al. 1982, 1984b, 1985, 1987a, 1987b, 1987c). The appearance of trichloroacetic acid in urine is not unique to 1,1,1-trichloroethane, as it has also been identified as a urinary metabolite of trichloroethylene and tetrachloroethylene (Monster 1988). If exposure is known to be solely to 1,1,1-trichloroethane, trichloroacetic acid levels in the urine may be a useful biomarker of exposure, because of the relatively long half-life of trichloroacetic acid. However, the length of time between 1,1,1-trichloroethane exposure and the measurement of breath, blood, or urine levels is critical to the accurate evaluation of the magnitude of exposure. Up to 90% of the 1,1,1-trichloroethane absorbed by any route is rapidly excreted unchanged in the expired air (Monster et al. 1979; Morgan et al. 1970, 1972b; Nolan et al. 1984; Stewart et al. 1961, 1969). Most of the remaining 10% is accounted for as the urinary metabolites trichloroethanol and trichloroacetic acid.

2.2 SUMMARY OF HEALTH EFFECTS

1,1,1-Trichloroethane is one of many solvents inhaled by some people to alter mood or consciousness. Available human and animal data indicate that the central nervous system is the most sensitive target for 1,1,1-trichloroethane toxicity. Clinical signs of toxicity associated with human exposure to large quantities of 1,1,1-trichloroethane include central nervous system depression, hypotension, cardiac arrhythmia, diarrhea and vomiting, mild hepatic effects, and dermal and ocular irritation. Deaths of persons exposed to high concentrations have been attributed to cardiac arrhythmia and respiratory failure secondary to central nervous system depression. Lower-level exposure to 1,1,1-trichloroethane may result in more subtle neurological effects such as impaired performance in tests designed to measure variables such as manual dexterity, eye-hand coordination, perceptual speed, and reaction time (Gamberale and Hultengren 1973; Mackay et al. 1987). Mild hepatotoxicity has been demonstrated in some animals exposed to relatively large quantities of 1,1,1-trichloroethane. Mild developmental effects induced by high level exposure of animals have not been verified in humans. Available data are inadequate to determine the carcinogenicity of 1,1,1-trichloroethane. The EPA has classified 1,1,1-tri-

chloroethane as group D, not classifiable as to human carcinogenicity, based on no reported human data and inadequate animal data (IRIS 2004). In general, route of exposure does not appear to be as important as circulating levels of 1,1,1-trichloroethane.

Death. The volatility of 1,1,1-trichloroethane, in addition to the rapid and extensive absorption and elimination of the inhaled compound, makes acute inhalation in product use situations the most likely lethal exposure scenario in humans. The acute lethal air concentration for humans is unknown; however, simulations of several lethal exposures suggest that it may be as low as 6,000 ppm (Droz et al. 1982; Jones and Winter 1983; Silverstein 1983). The results of animal studies indicate that the acute lethal exposure concentration decreases substantially with increasing exposure duration. Thus, the concentration required to cause animal death after a 6–7-hour exposure is 3–4 times less than that required after a 15-minute exposure (Adams et al. 1950; Bonnet et al. 1980; Clark and Tinston 1982; Gradiski et al. 1978).

Human deaths after inhalation exposure to 1,1,1-trichloroethane have been attributed to respiratory failure secondary to central nervous system depression and to cardiac arrhythmias (Guberan et al. 1976; Hall and Hine 1966; Jones and Winter 1983; MacDougall et al. 1987; Stahl et al. 1969; Travers 1974; Winek et al. 1997). Animal studies reveal that arrhythmias may result from sensitization of the heart to epinephrine (Carlson 1981; Clark and Tinston 1973; Kobayashi et al. 1982; Reinhardt et al. 1973). Hypoxia may exacerbate the situation (Reinhardt et al. 1971). Therefore, acute lethal exposure levels may be lower in individuals exposed during physical exertion (King et al. 1985; Ranson and Berry 1986; Troutman 1988). Physical exertion also may decrease the acute lethal exposure level by increasing the respiratory rate and lung perfusion rate, thereby increasing the systemic absorption of 1,1,1-trichloroethane.

Very little is known about the lethality of ingested 1,1,1-trichloroethane in humans. In one case of acute oral exposure, accidental ingestion of 600 mg/kg of 1,1,1-trichloroethane was not fatal (Stewart and Andrews 1966). Animal studies suggest that even higher acute oral doses may not cause death (Kinkead and Wolfe 1992; Torkelson et al. 1958).

Neurological Effects. Neurological effects are the preeminent signs of acute inhalation exposure to 1,1,1-trichloroethane in humans. The intoxicating effects of the inhaled chemical create a potential for its abuse. The severity of central nervous system depressant effects in humans during acute inhalation exposure increases as the exposure duration and level are increased. Impaired performance of

psychophysiological function tests has been observed in individuals exposed to moderate concentrations (≥175 ppm) (Gamberale and Hultengren 1973; Mackay et al. 1987). The Mackay et al. (1987) study served as the basis for derivation of the acute-duration inhalation minimal risk level (MRL). Dizziness, lightheadedness, and loss of coordination are caused by exposure to higher concentrations (>500 ppm) (Stewart et al. 1961, 1969; Torkelson et al. 1958). General anesthesia occurs at high levels (≥10,000 ppm) (Dornette and Jones 1960). These effects subside rapidly after exposure. One report suggested that impaired memory and deficits in balance were persistent effects in a group of workers after chronic exposure to moderate to high levels of 1,1,1-trichloroethane (Kelafant et al. 1994).

Animals are useful models for examining the neurological effects of exposure to 1,1,1-trichloroethane. As in humans, central nervous system depression is the predominant effect of inhaled 1,1,1-trichloroethane. Signs include ataxia, unconsciousness, and death at increasing concentrations (Bonnet et al. 1980; Clark and Tinston 1982; Evans and Balster 1993; Gehring 1968; Hougaard et al. 1984; Lazarew 1929). No evidence of gross or histological damage was found in the brains of most exposed animals, although some evidence of potential for cellular damage was indicated by reports of increased levels of glial fibrillary acid protein and decreased DNA content in the brain of gerbils after repeated exposure to low levels of the chemical (Karlsson et al. 1987; Rosengren et al. 1985). The Rosengren et al. (1985) study served as the basis for the intermediate-duration inhalation MRL. Alterations of brain metabolism also were observed in exposed animals (Folbergrova et al. 1984; Hougaard et al. 1984; Nilsson 1986a, 1986b; You and Dallas 2000). Behavioral changes, including impaired performance of neurobehavioral tests and increased motor activity, have been widely reported (Halogenated Solvents Industry Alliance 1991; 1990 Balster et al. 1982, 1997; Bowen and Balster 1996, 1998; DeCeaurriz et al. 1983; Geller et al. 1982; Horiguchi and Horiguchi 1971; Kjellstrand et al. 1985a; Mattsson et al. 1993; Moser and Balster 1985, 1986; Moser et al. 1985; Mullin and Krivanek 1982; Páez-Martínez et al. 2003; Warren et al. 1997, 1998; Wiley et al. 2002; Woolverton and Balster 1981; You et al. 1994); however, the sites of action and biochemical mechanisms of neurotoxicity have not been identified. Neurophysiological changes also have been reported (Halogenated Solvents Industry Alliance 1991). These latter observations were made at a relatively high exposure level (4,000 ppm). 1990 (could not confirm)

The study of You, et al., 1994 suggests that reduction in brain cyclic GMP levels may be responsible for the behavioral changes associated w/ 1,1,1-trichloroethane toxicity. This should be mentioned.

Little information was located regarding neurological effects in humans or animals after oral or dermal exposure to 1,1,1-trichloroethane. Existing data indicate that a single oral exposure to a dose of approximately 600 mg/kg did not produce overt signs of neurotoxicity (Stewart and Andrews 1966). It is assumed, however, that sufficiently high doses of 1,1,1-trichloroethane administered orally or dermally

will result in neurological effects. Oral exposure to 1,1,1-trichloroethane produced neurophysiological changes in rats given moderate doses (700 mg/kg/day) (Spencer et al. 1990) and gross neurobehavioral changes (hyperexcitability and narcosis) in rats given high doses (≥2,500 mg/kg/day) (Bruckner et al. 2001). No neurological effects were observed in the offspring of rats treated by gavage during gestation and lactation with up to 750 mg 1,1,1-trichloroethane/kg/day (Dow Chemical 1993) (see Developmental Effects). No clinical signs of neurotoxicity were seen in rats and mice receiving 1,1,1-trichloroethane in the diet at concentrations as high as 80,000 ppm (doses as high as 4,800 and 5,000 mg/kg/day in males and females, respectively) for 13 weeks (NTP 2000).

Cardiovascular Effects. 1,1,1-Trichloroethane can lower blood pressure (mildly to severely) in humans (Dornette and Jones 1960; Krantz et al. 1959) and can induce transient myocardial injury (Wodka and Jeong 1991). Such effects, however, are likely only after exposure to very high concentrations of 1,1,1-trichloroethane vapor. Chronic exposure of workers to levels ≤250 ppm did not affect blood pressure, heart rate, or electrocardiogram results in humans (Kramer et al. 1978). Reduced blood pressure accompanies exposure to anesthetic concentrations of 1,1,1-trichloroethane vapor (10,000–26,000 ppm). The effects are not permanent and subside shortly after exposure. The hypotensive mechanism has been studied in animals and appears to involve cardiac depression and peripheral vasodilation (Herd et al. 1974).

Human deaths following 1,1,1-trichloroethane inhalation are often attributed to cardiac arrhythmias (Guberan et al. 1976; MacDougall et al. 1987; Travers 1974). Such conclusions are based on animal studies in which arrhythmias have been produced during or immediately following acute inhalation exposure to 1,1,1-trichloroethane (Carlson 1981; Clark and Tinston 1973; Reinhardt et al. 1973; Trochimowicz et al. 1974). The mechanism for the arrhythmias apparently involves sensitization of the heart to endogenous epinephrine. The exposure level at which cardiac sensitization occurs in humans is not known, but in animals, concentrations as low as 5,000 ppm are effective after only 10 minutes of inhalation (Reinhardt et al. 1973). Physical exertion, stress, or any other stimulus of epinephrine release from the adrenal medulla may render an individual more vulnerable to 1,1,1-trichloroethane. Hypoxia may further increase a subject's susceptibility.

Hepatic Effects. 1,1,1-Trichloroethane may be a mild hepatotoxin in humans, although the evidence is not conclusive. Increased levels of serum bilirubin, lactate dehydrogenase (LDH), alkaline phosphatase, and serum glutamic oxaloacetic transaminase (SGOT), all suggestive of liver injury, have

been reported in humans exposed to high levels of 1,1,1-trichloroethane by inhalation or ingestion (Halevy et al. 1980; Hodgson et al. 1989; Stewart and Andrews 1966). Elevated serum LDH, gamma-glutamyl transpeptidase (GGT), SGOT, and glutamic pyruvic transaminase (SGPT), and pathologic signs of progressive liver disease were noted in a patient who was occupationally exposed to 1,1,1-trichloroethane for several years (Cohen and Frank 1994). Removal of the patient from exposure resulted in improvement of the impaired liver function. Mild hepatic changes have also been found by liver biopsy in exposed individuals and at autopsy in individuals who died after acute inhalation exposure to high concentrations of 1,1,1-trichloroethane (Caplan et al. 1976; Halevy et al. 1980; Hall and Hine 1966; Hodgson et al. 1989). Animals studies indicate that exposure to relatively high 1,1,1-trichloroethane concentrations in air (≥1,000 ppm) or high oral doses (≥1,334 mg/kg) are required to produce liver injury (Adams et al. 1950; Bruckner et al. 2001; Calhoun et al. 1981; McNutt et al. 1975; NTP 1996, 2000; Torkelson et al. 1958; Tyson et al. 1983). Effects observed in animals include necrosis, fatty change, increased liver weight, and changes in liver and serum enzyme levels. These effects are reversible and subside after termination of exposure (in the case of necrosis, hepatocytes in the proximity of the killed cells proliferate and replace them).

Developmental Effects. Developmental effects in humans exposed to 1,1,1-trichloroethane have not been observed. Epidemiology studies found no relationship between adverse pregnancy outcomes and maternal exposure to 1,1,1-trichloroethane (Deane et al. 1989; Lindbohm et al. 1990; Swan et al. 1989; Taskinen et al. 1989; Windham et al. 1991; Wrensch et al. 1990a, 1990b). Minor embryotoxic effects were observed in rats and rabbits after inhalation exposure to high concentrations of 1,1,1-trichloroethane (BRRC 1987a, 1987b; York et al. 1982). Effects included decreased fetal weights, increased minor soft tissue and skeletal anomalies, and delayed ossification. Exposure of pregnant mice to 1,1,1-trichloroethane at a concentration of 2,000 ppm for 17 hours/day on gestation days 12–17 resulted in significantly reduced postnatal pup weights, overt developmental delays (pinnae detachment, incisor eruption, eye opening), and impaired performance in behavioral tests (righting reflex, forelimb grip strength, negative geotaxis, inverted screen climbing) (Jones et al. 1996). In a similar study of pregnant rats that were exposed to 7,000 ppm of 1,1,1-trichloroethane 3 times/day for 60 minutes on gestation days 13–19, two of nine litters were completely resorbed and significant increases in gestation length were noted. Developmental effects included increased mortality at birth, decreased litter weight, and significant deficits in coordination, muscle strength, and spontaneous motor activity (Coleman et al. 1999). The developmental defects reported in three of these studies (BRRC 1987a, 1987b; Coleman et al. 1999) may have been associated with significant maternal toxicity. Neither an inhalation study using a lower,

although still high, concentration (Schwetz et al. 1975) nor drinking water studies (George et al. 1989; Lane et al. 1982; NTP 1988a, 1988b) revealed any developmental effects. Furthermore, a comprehensive study in which pregnant rats were gavaged with 1,1,1-trichloroethane during gestation and lactation found no neurobehavioral alterations in the pups tested up to 2 months of age (Dow Chemical 1993). Overall, 1,1,1-trichloroethane does not appear to be a significant developmental toxicant in animals. However, in view of the known neurological effects of 1,1,1-trichloroethane in humans and animals, additional developmental studies that examine neurological end points would be an important component of a complete investigation of 1,1,1-trichloroethane's potential developmental toxicity in humans.

Cancer. A relationship between exposure to 1,1,1-trichloroethane and cancer in humans has not been established. Among animals, no effects were found in a well-designed inhalation study at exposure levels ≤1,500 ppm (Quast et al. 1988). The results of an oral study indicate that 1,1,1-trichloroethane may have increased the occurrence of immunoblastic lymphosarcoma in rats; however, the biological and statistical significance of these results are questionable because of the study design limitations (Maltoni et al. 1986). The results of another oral (gavage) cancer bioassay (NCI 1977) were negative, but high early mortality in treated animals in this study made these results questionable.

Information is also limited on the role of 1,1,1-trichloroethane metabolites in the compound's toxicity. Reactive metabolites are important in the carcinogenicity of other chloroethanes (i.e., 1,1,2,2-tetrachloroethane). Binding to DNA, which is correlated with carcinogenicity in chlorinated ethanes (Lattanzi et al. 1988), was weak in an *in vivo* test (Turina et al. 1986). Even weak binding, however, indicates the potential to interact with DNA. Cell biotransformation tests were positive for this chemical (Daniel and Dehnel 1981; Hatch et al. 1982, 1983; Milman et al. 1988; Price et al. 1978; Tu et al. 1985). The results of these assays may have been confounded by the presence of stabilizing agents, however. Two of the common stabilizing additives in commercial formulations of 1,1,1-trichloroethane are 1,2-epoxybutane (butylene oxide) and 1,4-dioxane (diethylene dioxide). Both stabilizers have been identified as animal carcinogens (NTP 1989a). At this time, it does not appear that 1,1,1-trichloroethane exposure poses a clear cancer risk in animals; however, as discussed above, the limitations of the available studies prevent a definitive assessment of the risk of cancer in humans exposed to the compound. Related to potential exposures near NPL hazardous waste sites, the risk appears to be of little significance.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

- An MRL of 2 ppm has been derived for acute-duration inhalation exposure (14 days or less) to 1,1,1-trichloroethane.

The acute-duration inhalation MRL is based on a lowest-observed-adverse-effect level (LOAEL) of 175 ppm for reduced performance of psychomotor tests in a human study by Mackay et al. (1987). Individuals exposed to 175 or 350 ppm of 1,1,1-trichloroethane for 3.5 hours demonstrated impaired performance of psychomotor tests. The derivation of this MRL is supported by results of other human studies. Gamberale and Hultengren (1973) found psychophysiological test performance deficits in exposed individuals, although at a higher concentration than the LOAEL of 175 ppm identified by Mackay et al. (1987). Muttray et al. (1999, 2000) found EEG changes consistent with increased drowsiness and slight irritant nasal responses in volunteers exposed to 200 ppm. Numerous studies described behavioral and neurophysiological effects in animals.

Although the LOAEL of 175 ppm in the critical study of Mackay et al. (1987) was associated with only a 3.5-hour exposure period, the acute-duration inhalation MRL is intended to be protective of a continuous acute-duration exposure. Data reported by Nolan et al. (1984) and Mackay et al. (1987) indicate that blood levels of 1,1,1-trichloroethane approach steady state during 2 hours of continuous inhalation exposure in humans. Neurobehavioral performance was correlated with 1,1,1-trichloroethane blood levels and there was little additional change in most measures of neurobehavioral performance as exposure duration increased from 2 to 3 hours (Mackay et al. 1987). Therefore, the LOAEL of 175 ppm was not adjusted for exposure duration.

- An MRL of 0.7 ppm has been derived for intermediate-duration inhalation exposure (15–364 days) to 1,1,1-trichloroethane.

The intermediate-duration inhalation MRL is based on a no-observed-adverse-effect level (NOAEL) of 70 ppm derived from the study by Rosengren et al. (1985), which found evidence of astrogliosis (increased glial fibrillary acid protein levels) in the brains of gerbils exposed to 210 or 1,000 ppm, but not 70 ppm, of 1,1,1-trichloroethane continuously for 3 months. Choice of a neurological end point for

the untreated controls (12, 16, 23, 22, and 33% lower in 5,000-, 10,000-, 20,000-, 40,000-, and 80,000-ppm groups, respectively). There were no indications of treatment-related clinical or histopathological effects. According to ATSDR policy, a treatment-related decrease in body weight of 10% or more and a 20% or greater decrease in body weight gain (relative to controls) may be considered to represent an adverse effect. The choice of 1,1,1-trichloroethane-induced body weight changes as the critical effect is supported by results of other subchronic- and chronic-duration oral and inhalation animal studies in which body weight effects were reported, either in the absence of other signs of toxicity (Adams et al. 1950; Bruckner et al. 2001; Prendergast et al. 1967) or at doses causing minimal liver lesions (Calhoun et al. 1981; Quast et al. 1978, 1988).

A total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to the NOAEL of 1,770 mg/kg/day for body weight effects in male mice administered 1,1,1-trichloroethane in the diet for 13 weeks.

Results of another intermediate-duration oral animal study were evaluated for the purpose of deriving an intermediate-duration oral MRL for 1,1,1-trichloroethane. Bruckner et al. (2001) reported a frank effect level (FEL) of 2,500 mg/kg (1,786 mg/kg/day when adjusted for exposure 5 days/week) for gross central nervous system depression and death in rats exposed by gavage. Investigation of systemic endpoints was limited to the liver; only mild hepatic changes were found and only at lethal doses. Sensitive neurological endpoints were not monitored. NTP (2000) observed no gross central nervous system effects or deaths at doses up to about 5,000 mg/kg-day in rats or 23,000 mg/kg/day in mice. The differences in the findings of the Bruckner et al. (2001) and NTP (2000) studies can be attributed to the bolus dosing employed by Bruckner et al. (2001). In comparison to relatively steady intake throughout the day in the diet, bolus dosing will produce much higher peak blood levels as the entire daily dose is rapidly absorbed. The gross central nervous system effects and mortality observed by Bruckner et al. (2001) are likely a reflection of the high peak blood levels by this mode of administration. Such bolus oral exposure is not considered relevant to longer-term or chronic exposure scenarios in humans. Therefore, the results of Bruckner et al. (2001) were not used as the basis for derivation of an intermediate-duration oral MRL for 1,1,1-trichloroethane.

A chronic-duration oral MRL was not derived for 1,1,1-trichloroethane. No relevant human data were located. Chronic-duration oral animal studies were designed as cancer bioassays and included only limited investigation of noncancer endpoints (Maltoni et al. 1986; NCI 1977).

indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for 1,1,1-trichloroethane. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity

reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

May want to point out that there are a disproportionate number of sniffing deaths in California and New York— is this population-related or something else?

3.2.1.1 Death

1,1,1-Trichloroethane is one of many solvents intentionally inhaled by some people to alter mood or consciousness. Solvent abuse of this type is associated with "sudden sniffing death" syndrome. In a survey of sudden sniffing deaths across the United States in the 1960s, 29 of the 110 deaths in the survey were attributed to inhalation of 1,1,1-trichloroethane (Bass 1970). Case reports of individuals who died following intentional inhalation of 1,1,1-trichloroethane are readily available (D'Costa and Gunasekera 1990; Droz et al. 1982; Guberan et al. 1976; Hall and Hine 1966; MacDougall et al. 1987; Ranson and Berry 1986; Travers 1974; Winek et al. 1997). 1,1,1-Trichloroethane is a widely used industrial solvent. Although mortality due to accidental exposure from its use as a solvent is not common, a number of cases have been reported (Caplan et al. 1976; Jones and Winter 1983; McCarthy and Jones 1983; Mercier 1977; Northfield 1981; Silverstein 1983; Stahl et al. 1969; Sullivan 1994).

Data from case reports and surveys are useful, but concomitant exposure to other chemicals cannot be ruled out, and exposure concentrations and durations are rarely known. Although the actual levels of exposure that produced death are not known for any of these cases, some investigators used simulations to estimate the fatal exposure concentrations. Droz et al. (1982) performed detailed simulations of two fatalities from intentional 1,1,1-trichloroethane inhalation. The lethal concentration of 1,1,1-trichloroethane was estimated to be between 6,000 and 14,000 ppm in one case and between 10,000 and 20,000 ppm in the other. Simulation of the circumstances of deaths of two people exposed while using 1,1,1-trichloroethane as a solvent showed that concentrations ≤6,400 ppm may have been generated in one case (Jones and Winter 1983) and concentrations ≤9,000 ppm may have been generated in the other (Silverstein 1983). Northfield (1981) reported a case in which a worker, whose death was attributed to respiratory failure, may have been exposed to 1,1,1-trichloroethane concentrations of 6,000 ppm or higher, depending on distance from the source.

Human death following acute exposure to high 1,1,1-trichloroethane concentrations is usually attributed to either depression of the central nervous system, which results in respiratory arrest (Hall and Hine 1966; Jones and Winter 1983; Stahl et al. 1969; Winek et al. 1997), or sensitization of the heart to epinephrine, which results in severe cardiac arrhythmias (Guberan et al. 1976; MacDougall et al. 1987; Travers 1974). The occurrence of death during physical exertion following inhalation of 1,1,1-trichloroethane (Ranson and Berry 1986) or a mixture of 1,1,1-trichloroethane and trichloroethylene (King et al. 1985; Troutman 1988) is consistent with the possibility that cardiac sensitization to epinephrine caused death in these cases. It should be noted that anoxia or hypoxia, which are present to some extent during physical exertion, exacerbate the cardiac arrhythmias caused by sensitization of the myocardium to catecholamines (Reinhardt et al. 1971).

Studies of animal mortality following acute inhalation exposure to 1,1,1-trichloroethane are numerous. Median lethal concentrations (LC_{50} values) have been calculated for rats and mice. For rats, LC_{50} values from 10,305 to 38,000 ppm were reported (Adams et al. 1950; Bonnet et al. 1980; Clark and Tinston 1982). For mice, reported LC_{50} values ranged from 3,911 to 22,241 ppm (Gradiski et al. 1978; Horiguchi and Horiguchi 1971; Moser and Balster 1985; Woolverton and Balster 1981). Much of the variation in these data can be attributed to differences in the exposure duration (higher LC_{50} values were generally obtained in studies with short exposure periods). In studies of the same duration, rats (6-hour LC_{50}=10,305 ppm) were somewhat more susceptible to 1,1,1-trichloroethane than mice (6-hour LC_{50}=13,414 ppm) (Bonnet et al. 1980; Gradiski et al. 1978). An alternative way to study lethality is to expose animals to a given concentration of vapor and record the time required to kill half of the animals (LT_{50}). The LT_{50} was 180 minutes in rats exposed to 18,000 ppm of 1,1,1-trichloroethane (Adams et al. 1950) and 595 minutes in mice exposed to 13,500 ppm (Gehring 1968). Deaths of animals exposed to 1,1,1-trichloroethane were usually attributed to either respiratory or cardiac failure (Adams et al. 1950; Clark and Tinston 1982; Krantz et al. 1959). Most deaths occurred during exposure. Animals that survived the exposure period usually recovered rapidly and appeared normal within 10–15 minutes (Adams et al. 1950; Clark and Tinston 1982).

1,1,1-Trichloroethane did not increase mortality in longer-term studies in which animals were exposed to lower exposure concentrations than the acute studies. No effects on survival were observed in intermediate-duration studies in which animals of several species were exposed to concentrations ≤5,000 ppm (Adams et al. 1950; Calhoun et al. 1981; Prendergast et al. 1967; Rosengren et al. 1985) or

chronic-duration studies in which rats and mice were exposed to concentrations ≤1,750 ppm (Quast et al. 1978; 1988).

Reliable acute LC_{50} values for death in each species are recorded in Table 3-1 and plotted in Figure 3-1. Acute exposure to high concentrations of 1,1,1-trichloroethane can be lethal to humans and animals. The cause of death is usually either respiratory or cardiac failure. Limited human data and studies in animals indicate that long-term exposure to low or moderate 1,1,1-trichloroethane concentrations may not influence survival.

3.2.1.2 Systemic Effects

Respiratory Effects. In humans, acute exposure to high concentrations of 1,1,1-trichloroethane can produce respiratory depression (Kelly and Ruffing 1993), leading to death (Hall and Hine 1966; Jones and Winter 1983; Stahl et al. 1969; Winek et al. 1997). Respiratory depression may be a result of generalized central nervous system depression (see the discussion of Neurological Effects in this section). Acute exposure to lower concentrations of 1,1,1-trichloroethane in controlled studies did not affect respiratory rate or volume in humans (Dornette and Jones 1960; Stewart et al. 1975; Torkelson et al. 1958). 1,1,1-Trichloroethane may act as a slight respiratory tract irritant, as evidenced by increased concentrations of proinflammatory cytokines in nasal secretions of healthy volunteers exposed to 1,1,1-trichloroethane at a vapor concentration of 200 ppm for 4 hours (Muttray et al. 1999). Chest radiographs from several (unspecified number) of 28 workers exposed to an undetermined concentration of 1,1,1-trichloroethane for about 10 years showed changes consistent with early pneumoconiosis (fibrosis), but this was consistent with known exposure to asbestos and silica (Kelafant et al. 1994).

Death due to respiratory failure has been reported in several species of animals acutely exposed to high 1,1,1-trichloroethane concentrations (Adams et al. 1950; Krantz et al. 1959). Other data on respiratory effects in animals are limited to results of histological examinations of the lungs and related tissues. Tissue lesions were not found in rats or dogs exposed to high concentrations of 1,1,1-trichloroethane for short periods (Adams et al. 1950; Bonnet et al. 1980; Cornish and Adefuin 1966; Herd et al. 1974). Exposure to moderate to high concentrations for intermediate periods (≤6 months) failed to produce pulmonary lesions in most species (Adams et al. 1950; Eben and Kimmerle 1974; MacEwen and Vernot 1974; Prendergast et al. 1967; Torkelson et al. 1958; Truffert et al. 1977), but irritation and inflammation

found widespread degenerative lipidic infiltration in the liver

occurred in the lungs of guinea pigs exposed to 1,000 ppm for 3 months (Torkelson et al. 1958). These effects were not found in other studies in which guinea pigs were exposed to lower concentrations or exposed for shorter durations (Adams et al. 1950; Prendergast et al. 1967; Torkelson et al. 1958). Rats and mice exposed to 2,000 ppm 1,1,1-trichloroethane for 3 months developed mild degeneration of the nasal olfactory epithelium (Calhoun et al. 1981). Chronic inhalation of moderate 1,1,1-trichloroethane concentrations did not produce lesions in the respiratory tissues of rats or mice (Quast et al. 1988).

The highest NOAEL values and all reliable LOAEL values for respiratory effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Although lung irritation, inflammation, and olfactory epithelium degeneration were found in some species of laboratory animals exposed for intermediate durations in some studies, the weight of evidence suggests that respiratory failure in humans and animals is secondary to central nervous system depression and occurs only after acute exposure to very high concentrations.

Cardiovascular Effects. Inhalation of very high 1,1,1-trichloroethane concentrations for a short period can produce severe cardiac arrhythmias and death in humans. Arrhythmias are thought to be produced indirectly by 1,1,1-trichloroethane by sensitization of the heart to epinephrine (Guberan et al. 1976; MacDougall et al. 1987; Travers 1974). Cardiac sensitization to epinephrine has also been demonstrated in animals exposed to 1,1,1-trichloroethane (Clark and Tinston 1973; Kobayashi et al. 1982). In addition, reduced blood pressure, occasionally severe, has been reported in humans following brief exposure to high concentrations of 1,1,1-trichloroethane (Dornette and Jones 1960; Krantz et al. 1959). Acute exposure to lower concentrations (<1,000 ppm) did not affect clinical cardiovascular parameters such as blood pressure, pulse, heart rate, or electrocardiogram in the humans tested (Gamberale and Hultengren 1973; Torkelson et al. 1958). Myocardial injury, monitored by electrocardiography and echocardiography, was reported in the case of a young male who inhaled typewriter correction fluid (Wodka and Jeong 1991). It should be noted, however, that 1,1,1-trichloroethane may have been only one of several chemicals in the correction fluid.

In humans, long-term exposure to high 1,1,1-trichloroethane vapor concentrations can have toxic effects on the heart that persist beyond the period of exposure. While experiments in animals have shown that arrhythmias produced by 1,1,1-trichloroethane and epinephrine quickly subside after the cessation of exposure (Carlson 1981; Clark and Tinston 1973), three human cases involved ventricular arrhythmias that persisted for 2 weeks or more after solvent exposure ended (McLeod et al. 1987; Wright and Strobl

1984). In all three cases, the subjects had been exposed repeatedly to high (unspecified) 1,1,1-trichloroethane concentrations. Echocardiograms revealed mild left ventricular dilation in one patient and slightly dilated left atrium in another, as well as impaired left ventricle function in both (McLeod et al. 1987). Chronic exposure (<250 ppm) to 1,1,1-trichloroethane had no effect on blood pressure, heart rate, or electrocardiogram in workers surveyed in a matched-pair epidemiology study (Kramer et al. 1978). Similar results were recently reported for a group of 28 workers exposed to unspecified, but high concentrations of 1,1,1-trichloroethane for about 10 years (Kelafant et al. 1994).

Sensitization of the heart to epinephrine-induced arrhythmias has been reported in both rabbits and dogs acutely exposed to high 1,1,1-trichloroethane concentrations (≥5,000 ppm) (Carlson 1981; Clark and Tinston 1973; Reinhardt et al. 1973; Trochimowicz et al. 1974). The effect is rapid, occurring after only a few minutes of exposure, and transitory, quickly disappearing after the end of exposure. In rabbits, there was evidence that susceptibility to arrhythmia increased with exposure duration, and that 1,1,1-trichloroethane itself, not its metabolites, produced the sensitizing effect (Carlson 1981). Among dogs, the effect was similar in normal animals and those with experimentally induced myocardial infarctions; prior damage to the heart did not lower the threshold for cardiac sensitization produced by 1,1,1-trichloroethane (Trochimowicz et al. 1974).

Blood pressure was reduced in dogs acutely exposed to high concentrations of 1,1,1-trichloroethane (>7,500 ppm) (Aoki et al. 1997; Herd et al. 1974; Krantz et al. 1959). This effect was studied in detail by Herd et al. (1974), who reported that the decrease in blood pressure began within 15 seconds of the start of exposure and grew more pronounced as exposure continued. At 8,000–15,000 ppm, the decrease in blood pressure was accompanied by increased myocardial contractility and cardiac output. A decrease in total peripheral resistance was apparently responsible for the decrease in blood pressure at these concentrations. At 20,000–25,000 ppm, blood pressure depression was caused by reductions in myocardial contractility and cardiac output. Blood pressure returned to pre-exposure values within 15 minutes after exposure, but indices of cardiac output and contractility required 45 minutes to recover. The dogs died if the blood pressure dropped too low. Histopathological changes in the heart were not found upon necropsy. In the study of Aoki et al. (1997), the decrease in blood pressure was accompanied by sinus tachycardia and increases in cardiac output, pulmonary vascular resistance, and pulmonary arterial pressure.

produce nausea and related symptoms in humans, but evidence from animals suggests that long-term exposure will not produce histological changes.

Hematological Effects. No evidence exists that 1,1,1-trichloroethane produces hematological effects in humans. Hematological parameters, including white blood cell count, red blood cell count, hemoglobin, and hematocrit, were unchanged in humans acutely exposed to high or moderate concentrations of 1,1,1-trichloroethane (Stewart et al. 1961, 1969, 1975; Torkelson et al. 1958; Wright and Strobl 1984). Hematological variables were similarly unaffected in workers chronically exposed to low-to-moderate levels of 1,1,1-trichloroethane in a matched-pair epidemiology study (Kramer et al. 1978). Hemolytic disease was suggested by increases in urinary urobilinogen in several people exposed to high levels of 1,1,1-trichloroethane (Stewart 1971; Stewart et al. 1961), but this possibility was discounted because there was no association between exposure and elevated urinary urobilinogen levels and because other indices of hematological effects were normal.

Hematological effects were not found in animals exposed to 1,1,1-trichloroethane. No exposure-related changes in hematological parameters were found following acute, intermediate, and chronic exposure to moderate to high 1,1,1-trichloroethane concentrations in several species of animals (Calhoun et al. 1981; Eben and Kimmerle 1974; Horiguchi and Horiguchi 1971; Koizumi et al. 1983; Krantz et al. 1959; MacEwen and Vernot 1974; Prendergast et al. 1967; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977).

The highest NOAEL values for hematological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Existing data indicate that 1,1,1-trichloroethane does not produce hematological effects in humans or animals following inhalation exposure.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to 1,1,1-trichloroethane.

No musculoskeletal effects were found in animals exposed to 1,1,1-trichloroethane as assessed by histopathological examination. No lesions were found in the muscles or bones of a monkey exposed to a high 1,1,1-trichloroethane concentration for 74 days (Adams et al. 1950), or in rats and mice exposed for intermediate- or chronic-durations to moderate to high concentrations of the chemical (Calhoun et al. 1981; Quast et al. 1988).

The highest NOAEL values for musculoskeletal effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Based on existing data, 1,1,1-trichloroethane does not cause musculoskeletal effects in animals after chronic inhalation exposure. The relevance of this information to human health is unknown.

Hepatic Effects. Although there were no indications of liver effects in studies of controlled human exposure to 1,1,1-trichloroethane, data from case reports of overexposed humans suggest that this chemical may produce hepatic effects in humans exposed to high levels.

Serum levels of transaminases and other enzymes, used as indicators of hepatocellular damage (or damage to other tissues or organ systems), were not increased by acute exposure to moderate to high 1,1,1-trichloroethane concentrations in controlled human studies; liver function tests were likewise unaffected (Dornette and Jones 1960; Stewart et al. 1961, 1969, 1971; Torkelson et al. 1958). However, some case studies of individuals exposed to high 1,1,1-trichloroethane concentrations did report elevated serum enzyme levels. Four individuals who had substantial occupational exposure to 1,1,1-trichloroethane had elevated serum glutamic oxaloacetic transaminase (SGOT) levels (Hodgson et al. 1989). An individual studied by Halevy et al. (1980) had elevated levels of serum bilirubin, lactate dehydrogenase (LDH), and alkaline phosphatase, as well as SGOT. It should be noted that SGOT and LDH are present in substantial amounts in myocardial cells as well as hepatocytes, and that elevations in these enzymes could have been the result of myocardial injury. Elevated serum LDH, gamma-glutamyl transpeptidase (GGT), SGOT, and glutamic pyruvic transaminase (SGPT), and pathologic signs of progressive liver disease were noted in a patient who was occupationally exposed to 1,1,1-trichloroethane for several years (Cohen and Frank 1994). Removal of the patient from exposure resulted in improvement of the impaired liver function, although the serum levels of these enzymes remained higher than normal. Other exposed individuals did not have elevated serum enzyme levels (Stewart 1971; Wright and Strobl 1984). In some cases, histopathological examination revealed mild fatty changes in the liver of individuals exposed to high 1,1,1-trichloroethane concentrations (Caplan et al. 1976; Hall and Hine 1966; Hodgson et al. 1989). In another case, cholestasis was observed (Halevy et al. 1980). Pathological liver effects were observed in two separate case reports of repeated exposure to 1,1,1-trichloroethane in poorly ventilated work areas (Croquet et al. 2003; Texter et al. 1979). Nevertheless, hepatic changes were not observed in most cases.

70% liver destruction - Abstract

Chronic exposure to low 1,1,1-trichloroethane levels (<250 ppm) did not affect serum chemistry parameters, including SGOT, SGPT, bilirubin, LDH, GGT, and alkaline phosphatase, in individuals tested as part of a matched-pair epidemiology study (Kramer et al. 1978). Results from tests for hepatic function were unremarkable in 28 workers exposed to unspecified, but high, concentrations of 1,1,1-trichloroethane for approximately 10 years (Kelafant et al. 1994).

1,1,1-Trichloroethane produces mild hepatic effects in animals. The primary effects reported are mild histopathological changes in the liver and effects on liver enzyme activities. Acute exposure to high 1,1,1-trichloroethane concentrations did not affect serum transaminase levels in rats or mice (Carlson 1973; Cornish and Adefuin 1966; Gehring 1968). An increase in transaminase levels would indicate damage to hepatocytes. The rate of deoxyribonucleic acid (DNA) synthesis in the liver also can be used as an indicator of hepatotoxicity. DNA synthesis would be expected to increase in response to cell death. Exposure to 1,100 ppm 1,1,1-trichloroethane produced a 67% increase in DNA synthesis in the livers of exposed rats after 1 week; DNA synthesis returned to control levels throughout the rest of the 15-week study (Truffert et al. 1977). Corresponding histopathological changes were not found throughout the study. Based on these data, measurement of DNA synthesis may be a more sensitive indicator of hepatocellular damage than increases in serum transaminase levels or the presence of readily observable lesions. However, these results have not been verified by additional testing. Only one study actually observed cell death following 1,1,1-trichloroethane exposure; occasional hepatocyte necrosis was seen in mice exposed to 1,000 ppm of 1,1,1-trichloroethane continuously for 14 weeks (McNutt et al. 1975). The first evidence of necrosis was not seen until after 10 weeks of exposure, but within 2 weeks of first occurrence, necrosis could be found in 40% of the exposed mice. In a study of chronic exposure, a slight decrease in the size of hepatocytes in the liver's portal region was seen in high-dose male and female rats at 6, 12, and 18 months, but these effects were not distinguishable from normal geriatric changes at 24 months (Quast et al. 1988).

The most widely reported hepatic effect in studies of 1,1,1-trichloroethane inhalation in animals is fat accumulation in the liver. Such changes are generally reversible and do not necessarily involve impairment of liver function. Histological examination following acute exposure to high concentrations revealed mild, reversible fatty changes in the livers of rats, but not dogs (Adams et al. 1950; Herd et al. 1974). Exposure duration was important in rats; effects were seen in those exposed for 7 hours, but not in those exposed to much higher concentrations for only 2 hours (Adams et al. 1950). In mice, 3-hour exposure to 800 ppm of 1,1,1-trichloroethane appeared to increase liver triglyceride levels, although

controls were not included (Takahara 1986a). In studies of intermediate duration, exposure to moderate to high 1,1,1-trichloroethane concentrations produced fatty changes in the livers of rats, mice, and guinea pigs (Adams et al. 1950; Calhoun et al. 1981; McNutt et al. 1975; Torkelson et al. 1958). Fatty changes produced by 1,1,1-trichloroethane in the livers of mice continuously exposed to 1,000 ppm for 14 weeks were described in detail by McNutt et al. (1975). Prominent swelling of centrilobular hepatocytes was visible after the first week of exposure. Swelling was associated with the presence of numerous small vesicles in the cytoplasm. After 4 weeks, the number of microbodies in the cytoplasm was dramatically increased, and lysosomal vesicles were more prominent. Increased liver triglyceride levels were also reported in this study.

Studies of 1,1,1-trichloroethane's effects on liver enzyme activity are inconclusive. Acute inhalation of high concentrations induced the activity of liver microsomal enzymes (e.g., cytochrome P-450, NADPH cytochrome c reductase) in rats and mice (Fuller et al. 1970; Lal and Shah 1970). Continuous exposure to low 1,1,1-trichloroethane levels for 10 days also increased microsomal enzyme activity in rats (Koizumi et al. 1983), but exhibited no effect on liver or red blood cell δ-aminolevulinic acid dehydratase (ALA-D) activity, inhibition of which is an early indicator for disruption of heme synthesis (Koizumi et al. 1984). A 5-day repeated exposure to a moderate concentration decreased microsomal cytochrome P-450 enzyme activity in rats (Savolainen et al. 1977). Intermediate-duration exposure to a moderate concentration had no effect on microsomal enzyme levels in rats (Toftgaard et al. 1981).

The highest NOAEL values and all reliable LOAEL values for hepatic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Mild to moderate hepatic effects were occasionally reported in humans and animals exposed to 1,1,1-trichloroethane. These include indications of fatty liver and, in one case, cholestasis in humans and manifestations of hepatic necrosis and fatty changes in animals. These changes were not found in many studies, and results were mixed in many studies that did show effects. Evidence of hepatocellular damage and necrosis, changes in liver enzyme activity, and fat accumulation generally were reported following exposure to high concentrations in acute- and intermediate-duration studies in animals. The severity of the effects appears to be related to exposure dose and duration. It is unclear whether 1,1,1-trichloroethane may induce or inhibit microsomal enzyme activity in rats. In any case, the implications of effects on liver enzyme activity for toxicity are not clear, mainly because of the contradictory nature of the reported results.

Renal Effects. A few studies in humans have examined 1,1,1-trichloroethane's effects on select parameters of serum and urine chemistry that are related to renal function. Evidence of renal impairment was found in only one case report (Halevy et al. 1980). The individual in this case, who was exposed for 4 hours in a small room without ventilation (probably to high levels) presented with proteinuria, elevated blood creatinine, and reduced creatinine clearance, all of which were maximal at time of admission and returned to normal within 10 days. In addition to having prominent renal effects, this individual was unusual in having prominent liver effects and only minimal neurological effects. The authors suggested that an individual hypersensitivity might explain the atypical course of 1,1,1-trichloroethane intoxication. No effects were found on subsequent evaluations. No evidence of nephrotoxicity was found in other studies, although the end points examined, such as blood urea nitrogen (BUN), are only adequate for detecting serious decrements in function. An increase in the BUN level would indicate decreased elimination of nitrogenous waste by the kidneys (impairment of kidney function). Acute exposure to 1,1,1-trichloroethane had no effect on BUN or uric acid levels in humans exposed to high or moderate concentrations (Stewart 1971; Stewart et al. 1969, 1975; Wright and Strobl 1984). Chronic-duration exposure of workers to <250 ppm of 1,1,1-trichloroethane had no effect on BUN, uric acid, or other serum indicators of nephrotoxicity in a matched-pair epidemiology study (Kramer et al. 1978).

Acute-duration exposure to high 1,1,1-trichloroethane concentrations failed to produce kidney lesions in rats (Adams et al. 1950; Bonnet et al. 1980; Cornish and Adefuin 1966; Krantz et al. 1959), although relative kidney weight was increased slightly at 12,000 ppm in the one study in which it was measured (Adams et al. 1950). Exposure of several animal species to moderate to high concentrations for intermediate durations had no apparent effect on kidney weight or histopathology, or relevant serum chemistry parameters (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Kjellstrand et al. 1985b; MacEwen and Vernot 1974; Prendergast et al. 1967; Torkelson et al. 1958; Truffert et al. 1977). Chronic inhalation of 1,1,1-trichloroethane did not affect the kidneys of rats or mice (Quast et al. 1988).

The kidney does not appear to be a target organ for 1,1,1-trichloroethane toxicity. The highest NOAEL values and all reliable LOAEL values for renal effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to 1,1,1-trichloroethane.

Information in animals is limited. In an acute-duration study, no histopathological changes were seen in the adrenals of rats after a single 2-hour exposure to up to 15,000 ppm 1,1,1-trichloroethane (Cornish and Adefuin 1966). Plasma corticosterone levels were statistically significantly decreased in rats after inhalation exposure to 1,1,1-trichloroethane at a concentration of 3500 ppm for 30 minutes or 5,000 ppm for 10 or 30 minutes; the highest exposure level also resulted in significantly reduced plasma adrenocorticotropic hormone (Pise et al. 1998). The NOAEL and LOAEL values for endocrine effects from these studies are recorded in Table 3-1 and plotted in Figure 3-1.

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Dermal Effects. Available information in humans is limited to a case-control report of significantly increased risk of systemic sclerosis (scleroderma) was associated with purported exposure to 1,1,1-trichloroethane in some Michigan women (Dow Corning Corp. 1994). However, a larger follow-up case-control study conducted on 660 women diagnosed with scleroderma between 1980 and 1992 in Michigan and Ohio found no significant association between exposure to 1,1,1-tricloroethane and scleroderma (Garabrant et al. 2003). In neither case control study could 1,1,1-trichloroethane exposure be quantified.

Mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane for 4 days exhibited dull fur coats (Evans and Balster 1993); this effect, however, was the result of direct contact with the chemical in the air (see Section 3.2.3.2). Intermittent exposure of rats or mice to 2,000 ppm 1,1,1-trichloroethane for 90 days (Calhoun et al. 1981) or to 1,500 ppm for 2 years (Quast et al. 1988) had no effect on the incidence of dermal lesions. NOAEL and LOAEL values derived from these studies are recorded in Table 3-1 and plotted in Figure 3-1.

Ocular Effects. Individuals briefly exposed to high 1,1,1-trichloroethane vapor concentrations reported mild eye irritation (Stewart et al. 1961). At moderate concentrations, no eye irritation was reported, even after 186 minutes.

Mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane for 4 days exhibited eye irritation during exposure (Evans and Balster 1993). All of the above effects, however, were probably due to direct contact of the chemical in the air with the eye (see Section 3.2.3.2). Intermittent exposure of rats or mice to 2,000 ppm 1,1,1-trichloroethane for 90 days (Calhoun et al. 1981) or to 1,500 ppm for 2 years (Quast et al. 1988) had no effect on the incidence of ocular lesions. NOAEL and LOAEL values derived from these studies are recorded in Table 3-1 and plotted in Figure 3-1.

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation exposure to 1,1,1-trichloroethane.

Acute inhalation exposure to high concentrations of 1,1,1-trichloroethane did not affect body weight in rats (Adams et al. 1950; Bonnet et al. 1980; Cornish and Adefuin 1966). However, mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane for 4 days experienced a 26% reduction in body weight throughout the exposure period (Evans and Balster 1993). In studies of intermediate duration, significant reductions in body weight gain were reported in guinea pigs exposed to 650 ppm (Adams et al. 1950) and rabbits and dogs exposed continuously to 377 ppm (Prendergast et al. 1967). Other intermediate-duration studies on a variety of species (including those mentioned above) found no compound-related effects on body growth, even at high concentrations (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Kjellstrand et al. 1985b; Kyrklund et al. 1988; MacEwen and Vernot 1974; Prendergast et al. 1967; Rosengren et al. 1985; Toftgaard et al. 1981; Torkelson et al. 1958; Truffert et al. 1977). Body weight gain was reduced in a concentration-dependent manner in female rats chronically exposed to 1,1,1-trichloroethane (Quast et al. 1988). Body growth was not affected in male rats or male or female mice chronically exposed to the same concentrations. Food consumption was not monitored in the available studies.

Changes in body weight can be produced in a number of ways (e.g., effects on palatability of food, absorption of nutrients, energy metabolism). In the case of 1,1,1-trichloroethane, it is possible that recurring central nervous system depression produced by repeated exposure may be responsible for the reduced body weight gain, by suppression of appetite and food intake. Due to the large number of factors that might affect body weight, assessing the potential relationship between isolated occurrences of reduced body weight gain in animals and possible effects of 1,1,1-trichloroethane on growth of humans is difficult. In any case, no effects from levels found near NPL hazardous waste sites would be expected. The highest NOAEL values and all reliable LOAEL values for body weight effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological effects in humans after inhalation exposure to 1,1,1-trichloroethane. However, lymphoreticular effects, specifically spleen congestion, have been observed at autopsy in cases of acute accidental exposure to high concentrations of 1,1,1-trichloroethane (Gresham and Treip 1983; Stahl et al. 1969).

The effect of acute inhalation of 1,1,1-trichloroethane vapor on immune response in mice was studied by Aranyi et al. (1986). Mice received a single 3-hour exposure to 359 ppm of 1,1,1-trichloroethane. Susceptibility to respiratory infection was tested by challenge with *Streptococcus zooepidemicus* during exposure. Mortality was similar in test and control mice, indicating no effect on susceptibility to bacteria. To test the effect of inhalation exposure to 1,1,1-trichloroethane on the bactericidal activity of alveolar macrophages, mice were exposed to radiolabeled 35S-*Klebsiella pneumoniae,* and the percentage of bacteria killed was recorded. No difference was found between test and control mice. The same results were found in both tests when mice were exposed under similar conditions for 5 days.

No histopathological alterations were observed in the spleen of rats exposed for 2 hours to up to 15,000 ppm 1,1,1-trichloroethane (Cornish and Adefuin 1966). Longer-term studies of immunological effects in animals exposed to 1,1,1-trichloroethane by inhalation were limited to gross and microscopic examination of the spleen, thymus, and lymph nodes. No effect on spleen weight or histopathology was reported among several species exposed to moderate to high 1,1,1-trichloroethane concentrations in studies of intermediate duration (Adams et al. 1950; Calhoun et al. 1981; Kjellstrand et al. 1985b; Prendergast et al. 1967; Torkelson et al. 1958). No exposure-related effects were found upon histopathological examination of the spleen and thymus after chronic exposure to ≤1,750 ppm in rats and 1,500 ppm in mice (Quast et al. 1978, 1988).

The highest NOAEL values for immunological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. The existing data suggest that 1,1,1-trichloroethane may not produce toxic effects on the immune system, but sensitive immunological end points have not been examined in humans or animals.

3.2.1.4 Neurological Effects

1,1,1-Trichloroethane produces central nervous system depression, increasing with exposure concentration from mild motor impairment to euphoria, unconsciousness, and death in humans. Low concentrations reportedly produce impaired performance in tests designed to measure variables such as manual dexterity, eye-hand coordination, perceptual speed, and reaction time (Gamberale and Hultengren 1973; Mackay et al. 1987). Results using subjective assessment techniques indicate that behavioral changes may not be apparent to those exposed. Syntactic reasoning remained intact, and distractibility actually improved in the study by Mackay et al. (1987), suggesting that impairment produced by 1,1,1-trichloroethane may be task-specific. In other studies, comparable exposure conditions did not produce significant psychomotor effects (Salvini et al. 1971) or produced only weak effects (Savolainen et al. 1981). Although these studies examined some of the same parameters, such as reaction time, different analytical methods were used and different subpopulations were tested. Laine et al. (1996) found no subjective symptoms and no significant effects on EEG, visual evoked potentials, or equilibrium among healthy male volunteers exposed to a time-weighted average concentration of 200 ppm of 1,1,1-trichloroethane for 5 hours, including six 10-minute periods of exercise. In another study, a 4-hour inhalation exposure of healthy male volunteers to 200 ppm of 1,1,1-trichloroethane resulted in significantly increased subjective tiredness scores and EEG changes consistent with increased drowsiness (Muttray et al. 2000). Based on the LOAEL of 175 ppm for reduced performance in psychomotor tests identified by Mackay et al. (1987), an acute inhalation MRL of 2 ppm was calculated as described in the footnote in Table 3-1.

Gross neurobehavioral effects, such as disturbances of equilibrium and coordination, occur in humans following acute exposure to 1,1,1-trichloroethane concentrations between 1,000 and 2,000 ppm (Stewart et al. 1961, 1969, 1975; Torkelson et al. 1958). These effects are more obvious at higher exposure concentrations (Torkelson et al. 1958). An increase was noted in the amplitude of alpha activity in electroencephalograms from individuals acutely exposed to moderate concentrations of 1,1,1-trichloroethane (Stewart et al. 1975). The significance of this effect is unknown, especially since it persisted for several days, but it occurred at an exposure level that produced no effect on equilibrium or coordination. Visual evoked response was not affected in this study. Complaints of lightheadedness were also reported at moderate levels (Stewart et al. 1961). High 1,1,1-trichloroethane concentrations are inhaled intentionally by some people to experience these and related effects of intoxication.

of 10 years revealed deficits in memory and in several components of balance (Kelafant et al. 1994); it was the investigators' opinion that the overall evidence was suggestive of toxic exposure. Deficits in memory, attention, and concentration were diagnosed in a 45-year-old male who had been heavily exposed to 1,1,1-trichloroethane, as well as dichloromethane, for 15 years (Garnier et al. 1991). Although the patient's brain function slowly improved following removal from exposure, lingering memory deficit was noted 5 years later.

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The principal neurological effects observed in animals exposed to 1,1,1-trichloroethane are signs of central nervous system depression, such as impaired performance in behavioral tests, ataxia, and unconsciousness, and are similar to those seen in humans. Relatively subtle behavioral effects in several species of animals have been reported following acute-duration exposure to 1,1,1-trichloroethane concentrations in the 700–14,000 ppm range (Halogenated Solvents Industry Alliance 1991; Balster et al. 1982, 1997; Bowen and Balster 1996, 1998; DeCeaurriz et al. 1983; Geller et al. 1982; Horiguchi and Horiguchi 1971; Kjellstrand et al. 1985a, 1990; Moser and Balster 1985, 1986; Moser et al. 1985; Mullin and Krivanek 1982; Páez-Martínez et al. 2003; Warren et al. 1997, 1998, 2000; Wiley et al. 2002; Woolverton and Balster 1981; You et al. 1994). These behavioral changes were readily reversible and generally involved effects on neuromuscular tests or learned behaviors. Studies using operant conditioning reflect effects of 1,1,1-trichloroethane in animals that are comparable to psychological changes in humans. Behavioral changes are generally considered to indicate neurological effects.

Neurophysiological changes have also been reported during acute-duration inhalation exposure to 1,1,1-trichloroethane (Halogenated Solvents Industry Alliance 1991). Exposure of rats to 2,000 ppm produced readily apparent changes in flash-evoked potential (FEP) and electroencephalogram (EEG), and more subtle changes in the somatosensory-evoked potential (SEP) when the rats were tested during exposure. Exposure to 1,000 ppm produced similar, but less marked, changes in the same measures. Continuous exposure of mice to moderate (500 ppm) concentrations of 1,1,1-trichloroethane for 4 days resulted in a withdrawal syndrome characterized by handling-induced seizures and reduced threshold to pentylenetetrazol-induced seizures after exposure ceased (Evans and Balster 1993). This effect could be prevented by central nervous system depressants, but not by anticonvulsants.

Acute-duration exposure to high 1,1,1-trichloroethane concentrations produced intoxication and incoordination in rats and mice (Adams et al. 1950; Clark and Tinston 1982; Hougaard et al. 1984; Lazarew 1929), and elevation of the threshold for pentetrazole-induced seizures in mice (DeCeaurriz et al.

1981). Exposure to 23,000 ppm produced ataxia, followed by unconsciousness and death due to respiratory failure in mice (Woolverton and Balster 1981). A progression from ataxia to lethargy, loss of motor function, and prostration produced by 1,1,1-trichloroethane has been observed in a variety of species, including rats, mice, dogs, and monkeys (Adams et al. 1950; Bonnet et al. 1980; Dow Chemical Co. 1988; Gehring 1968; Krantz et al. 1959; Lazarew 1929; Torkelson et al. 1958).

A comprehensive 13-week neurotoxicity study in rats included grip strength measures, a battery of observational measures, an electrophysiological test battery, and a neuropathology examination (Mattsson et al. 1993). The only notable finding was a significant deficit in forelimb grip performance in both male and female rats exposed to high levels (2,000 ppm) that persisted at least 7 weeks beyond the end of the exposure period. Histopathological and electrophysiological studies found no evidence of neuropathy in the forelimb that might account for this result. The authors hypothesized that sedative properties of 1,1,1-trichloroethane may have been responsible by allowing the animals to become more relaxed and, consequently, more habituated to the test procedure. No effects were found at moderate levels (630 ppm). The lack of neurophysiological effects at concentrations that produced such effects in the acute-duration study by Halogenated Solvents Industry Alliance (1991) reflects the fact that testing was performed during exposure in the acute-duration study and 65 hours after the end of exposure in the intermediate-duration study.

Histopathological changes in the brain and spinal cord are not characteristic of 1,1,1-trichloroethane exposure and have not been reported when these structures have been examined (Herd et al. 1974; Krantz et al. 1959; Mattsson et al. 1993; Prendergast et al. 1967; Quast et al. 1978, 1988); however, researchers who have subjected gerbils to continuous, intermediate-duration exposure to 1,1,1-trichloroethane have reported changes in the brain that indicate physical damage. Four months after exposure had been discontinued, there was a significant increase in the level of glial fibrillary acid (GFA) protein in the sensorimotor cerebral cortex following exposure to 210 ppm of 1,1,1-trichloroethane (Rosengren et al. 1985). Since this protein is the main protein subunit of astroglial filaments and is found mainly in fibrillary astrocytes, an increase in its occurrence indicates the formation of astroglial fibrils, which are formed in response to brain injury. Therefore, increased GFA protein is associated with astrogliosis and central nervous system damage. These changes produced by 1,1,1-trichloroethane in this study were irreversible, or at least persistent. An intermediate-duration inhalation MRL of 0.7 ppm was derived for 1,1,1-trichloroethane based on the results of this study, as described in the footnote in Table 3-1. A second study, in which gerbils were exposed to 70 ppm of 1,1,1-trichloroethane by the same protocol, was

conducted by Karlsson et al. (1987). DNA content was used to measure cell density in different parts of the brain following exposure. Significantly decreased DNA content was found in the posterior cerebellar hemisphere, anterior cerebellar vermis, and hippocampus. These results could be caused by decreased cell density, possibly because of cell loss either by cell death or inhibition of nonneuronal cell acquisition in these areas, but the significance of these changes is uncertain. These methods of ascertaining physical damage to the brain have not been applied to other species.

1,1,1-Trichloroethane also produced changes in brain metabolism in rats and mice. Folbergrova et al. (1984) found a number of changes in cerebral cortical metabolism in rats exposed to high levels. Decreased glucose consumption and blood flow have also been documented in rats (Hougaard et al. 1984). Exposure of rats and mice to low-to-moderate 1,1,1-trichloroethane concentrations resulted in altered brain levels of cyclic nucleotides (Nilsson et al. 1986a, 1986b; You and Dallas 2000). The importance of the effects on cyclic nucleotides may lie in their altered capacity to act as secondary messengers within the cells, although the toxicological significance of this effect is unknown. No effect on the levels of protein, glutathione, acid proteinase, or ribonucleic acid (RNA) in the brain was found in rats acutely exposed to low concentrations of 1,1,1-trichloroethane (Savolainen et al. 1977). Continuous exposure to 1,200 ppm, but not lower doses, of 1,1,1-trichloroethane for 30 days altered the fatty acid composition of ethanolamine phosphoglyceride isolated from the cerebral cortex in rats (Kyrklund and Haglid 1991; Kyrklund et al. 1988).

1,1,1-Trichloroethane may share discriminate-stimulus properties with both pentobarbital and ethanol (Rees et al. 1987a, 1987b). Rees et al. (1987a) trained mice to press one lever in response to pentobarbital injection and another in response to saline injection. In this way, mice could "tell" the investigator when they were injected with pentobarbital. Upon inhalation of 1,1,1-trichloroethane for 20 minutes, there was a concentration-dependent increase in the percentage of time mice pressed the pentobarbital lever, indicating that the mice were generalizing the effects of pentobarbital to those of 1,1,1-trichloroethane. The results were similar in the second study (Rees et al. 1987b), in which the mice were trained to discriminate between ethanol and saline, and then exposed to 1,1,1-trichloroethane. These studies suggest that mice did not discriminate between the neurological effects of moderate to high concentrations of 1,1,1-trichloroethane and those of pentobarbital and ethanol.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. The acute depressive effect of

1,1,1-trichloroethane in both humans and animals progresses from subtle behavioral effects at low-to-moderate concentrations to unconsciousness at high concentrations. There is evidence to suggest that 1,1,1-trichloroethane does not produce permanent neurological effects in humans. A study in gerbils, however, has produced evidence of lasting physical damage to the nervous system (astrogliosis) following prolonged continuous exposure to low concentrations (210 ppm) of this chemical. More data are needed to determine whether these results/observations are relevant for determining human risk.

3.2.1.5 Reproductive Effects

Limited information is available regarding the reproductive toxicity of 1,1,1-trichloroethane in humans, and exposure levels have not been quantified. Taskinen et al. (1989) conducted a case-control epidemiology study to investigate the relationship between adverse pregnancy outcomes (spontaneous abortions and congenital malformations) and occupational exposure of fathers to organic solvents, including 1,1,1-trichloroethane, during spermatogenesis for the 80 days prior to conception. No relationship was found between exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes. An apparent decrease in fertility (as measured by number of menstrual cycles required for wife to become pregnant) was noted in Finnish male workers with exposure to 1,1,1-trichloroethane, but the difference from controls was not statistically significant (Sallmén et al. 1998).

Studies in several animal species found no evidence that 1,1,1-trichloroethane has adverse reproductive effects. Histological examination of male and female reproductive tissues following acute-, intermediate-, and chronic-duration exposure to 1,1,1-trichloroethane revealed no exposure-related changes in rats, mice, or rabbits (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977); however, varying degrees of testicular degeneration were observed in male guinea pigs exposed to 5,000 ppm 1,1,1-trichloroethane for 45 days (Adams et al. 1950). One intermediate-duration study used blood chemistry analyses to determine reproductive effects. Continuous exposure to moderate levels of 1,1,1-trichloroethane vapor had no effect on butyrylcholinesterase activity in mice, which suggests that exposure did not have any effect on testosterone activity (Kjellstrand et al. 1985b). Testosterone appears to play a major role in regulating butyrylcholinesterase activity, and, although activity of this enzyme may change in the absence of an effect on testosterone, it is unlikely that an effect on testosterone levels would not be reflected by a change in butyrylcholinesterase activity.

The highest NOAEL values for reproductive effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Based on the existing data, the reproductive system does not appear to be a target of 1,1,1-trichloroethane toxicity following inhalation exposure; however, the reproductive toxicity of this chemical cannot be evaluated fully due to the limited human data available and the lack of inhalation studies of reproductive function in animals.

3.2.1.6 Developmental Effects

Several case-control epidemiology studies investigated the relationship between adverse pregnancy outcomes (spontaneous abortions and/or congenital malformations) and maternal exposure to solvents, including 1,1,1-trichloroethane (Lindbohm et al. 1990; Taskinen et al. 1989; Windham et al. 1991). No clear evidence of a relationship between exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes was found in any of these studies.

The potential developmental toxicity of inhaled 1,1,1-trichloroethane has been examined in rats and mice. Schwetz et al. (1975) exposed pregnant females of both species to moderate concentrations of 1,1,1-trichloroethane on days 6–15 of gestation. The only significant finding was an increase in absolute liver weight of maternal rats but not of maternal mice. Indices of embryo/fetotoxicity were comparable to controls. York et al. (1982) exposed female rats to 2,100 ppm of 1,1,1-trichloroethane for 2 weeks prior to mating and/or throughout pregnancy. There were no signs of maternal toxicity in any test group. A significant decrease in fetal body weight was observed in groups exposed either before and during pregnancy or during pregnancy only. Fetal body weights were not affected in the group exposed to 1,1,1-trichloroethane before pregnancy only. A significant increase in the incidence of delayed ossification and soft-tissue anomalies was observed only in the group that was exposed during both the premating period and gestation. Pup survival and weight gain were not affected by treatment, and neither was pup performance on neurobehavioral tests. There was no evidence of gross lesions upon necropsy at 12 months. Exposure of pregnant rats to 6,000 ppm of 1,1,1-trichloroethane during gestation days 6–15 decreased fetal weight and delayed ossification of the cervical centrum (BRRC 1987a). Signs of maternal toxicity at this concentration included hypoactivity during exposure, perioral wetness, decreased food consumption, and increased water consumption. Maternal toxicity may have contributed to the fetotoxicity observed. Maternal toxicity and fetotoxicity were not observed in rats exposed to 3,000 ppm.

Pregnant rabbits exposed to 6,000 ppm of 1,1,1-trichloroethane during gestation days 6–18 had decreased weight gain during exposure (BRRC 1987b). A significant increase in the incidence of extra ribs was noted in the fetuses; however, this is an anomaly often associated with maternal toxicity, regardless of the test agent. No other evidence of embryotoxicity or teratogenicity was observed in this study.

Exposure of pregnant mice to 1,1,1-trichloroethane at a concentration of 2,000 ppm for 17 hours/day on gestation days 12–17 resulted in significantly reduced litter and postnatal pup weights, overt developmental delays (pinnae detachment, incisor eruption, eye opening), and impaired performance in behavioral tests (righting reflex, forelimb grip strength, negative geotaxis, inverted screen climbing) (Jones et al. 1996). There were no clinical signs of maternal toxicity and no statistically significant effects on number of litters, gestation length, litter size, number of live male or female pups per litter, or spontaneous motor activity, relative to controls. Other pregnant mice were exposed to 8,000 ppm 3 times/day for 60 minutes on gestation days 12–17 (Jones et al. 1996). Dams were nearly anesthetized during exposure and exhibited mild tremors and gait abnormalities during observational battery testing. Significantly reduced postnatal pup weight, developmental delays (pinnae detachment, incisor eruption, eye opening), and impaired performance in behavioral tests (righting reflex, forelimb grip strength, negative geotaxis, rooting reflex) were noted. In a similar study of pregnant rats, exposed to 7,000 ppm of 1,1,1-trichloroethane 3 times per day for 60 minutes on gestation days 13–19, maternal weight gain was significantly reduced during the exposure period and dams exhibited clinical signs that included salivation, lacrimation, and abnormal gait (Coleman et al. 1999). Litters were completely resorbed in two of nine exposed dams and significant increases in gestation length were noted. Developmental effects included increased mortality at birth, decreased litter weight, and significant deficits in coordination, muscle strength, and spontaneous motor activity.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. These data suggest that 1,1,1-trichloroethane is not a potent developmental toxin. Minor developmental effects characteristic of developmental delay were reported only at high doses and were usually accompanied by maternal toxicity.

3.2.1.7 Cancer

In case-control studies, occupational exposure to 1,1,1-trichloroethane was not found to be associated with astrocytic brain cancer (Heineman et al. 1994), renal cell carcinoma (Dosemeci et al. 1999), pancreatic cancer (Kernan et al. 1999), or esophageal or stomach cancer (Rohr Indus Inc. 1987a; Rohr Indus Inc. 1987b). There was no significant correlation between release of 1,1,1-trichloroethane in 26 Florida counties in 1987 and age adjusted incidence of childhood brain tumors in these counties in 1992–1993 (Mulla 1996). Statistically significantly increased standardized incidence ratios for cancer of the nervous system and multiple myeloma were reported in male and female Finnish workers exposed to 1,1,1-trichloroethane (Anttila et al. 1995). However, the finding is based on only three cases of nervous system tumors and two cases of multiple myeloma, and most of the workers were exposed to other solvents as well. An increased risk of multiple myeloma was also observed in a cohort of female workers in Utah, but no association was found between non-Hodgkin's lymphoma and 1,1,1-trichloroethane exposure in these workers (Spirtas et al. 1991). The results, however, are questionable because only two cases of multiple myeloma were observed and the women were also exposed to many other chemicals. Based on the limited human data, it is not known whether inhaled 1,1,1-trichloroethane presents a human carcinogenicity concern.

A study of 1,1,1-trichloroethane vapor carcinogenicity in Fischer 344 rats and B6C3F1 mice was conducted by Quast et al. (1988). Animals were chronically exposed to moderate to high concentrations (150–1,500 ppm) of the chemical. In rats, no significant differences in survival were observed between groups. Body weights of treated and control rats were comparable except for a slight but significant decrease in high-dose females. Slight microscopic changes were seen in the livers of high-dose male and female rats at 6, 12, and 18 months, but these effects were not distinguishable from normal geriatric changes at 24 months. In mice, no significant differences in survival, growth, or incidence of nonneoplastic lesions were observed between groups. Pairwise comparisons between control and treated groups revealed no differences in the incidence of tumors in rats or mice. Two positive dose-related trends were statistically significant, but neither was considered treatment related. In male rats, a positive trend was evident for the incidence of benign bilateral interstitial cell tumors of the testes, a highly spontaneous tumor in the strain of rats tested. This trend disappeared when all interstitial cell tumors were combined and re-analyzed. A statistically significant trend was found for an increase in the combined incidence of benign adenomas and cystadenomas in the lacrimal gland of female mice, but the incidences were statistically comparable to concurrent controls as well as within the historical control

range. The authors point out there was no increase in the incidence of lymphoreticular proliferative processes in either species in this study. This study adequately demonstrated no evidence of carcinogenicity by the inhalation route at the exposure levels used, which approach the maximum tolerated dose (MTD). An apparent increase in the occurrence of immunoblastic lymphosarcomas of the lung was reported in rats tested in an oral carcinogenicity study (Maltoni et al. 1986), described in Section 3.2.2.8.

3.2.2 Oral Exposure

3.2.2.1 Death

A single report of human oral exposure to 1,1,1-trichloroethane was found in the literature. A man survived after accidentally drinking a single ≈600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966). Clinical signs of toxicity were limited to a burning sensation in the throat, nausea, and incapacitating vomiting and diarrhea.

Torkelson et al. (1958) reported acute oral LD_{50} values of 12,300 and 10,300 mg/kg for male and female rats, respectively. LD_{50} values for other species include 11,240 mg/kg for mice, 9,470 mg/kg for guinea pigs, and 5,660 mg/kg for rabbits (Torkelson et al. 1958). A more recent study reported LD_{50} values of 17,148 and 12,996 mg/kg for male and female mice, respectively (Kinkead and Wolfe 1992). In 6-week studies, lethality was produced by gavage doses of 5,620 mg/kg/day in rats and 10,000 mg/kg/day in mice (NCI 1977). Repeated gavage doses of 2,500 mg/kg/day resulted in high rates of mortality within 50 days (Bruckner et al. 2001). Larger doses (≥5,000 mg/kg/day) for shorter time periods (11 days or less) were even more lethal (Bruckner et al. 2001). In chronic studies, effects on survival occurred at much lower doses. Survival decreased in rats exposed to 750 mg/kg/day and mice exposed to 2,807 mg/kg/day by gavage (NCI 1977). Chronic oral exposure to 500 mg/kg/day of 1,1,1-trichloroethane by gavage did not affect rat survival (Maltoni et al. 1986). Survival of rats and mice was not affected by administration of 1,1,1-trichloroethane in the diet at concentrations as high as 80,000 ppm (approximate doses as high as 5,000 and 23,000 mg/kg/day, respectively) for 13 weeks (NTP 2000).

Exposure to high oral doses of 1,1,1-trichloroethane can be lethal to animals and, presumably, to humans. The levels associated with decreased survival in animals appeared to decrease as exposure duration

increased. Reliable LD_{50} and LOAEL values for death are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration are recorded in Table 3-2 and plotted in Figure 3-2.

No reports were located in which endocrine, ocular, or metabolic effects were associated with oral exposure of humans or animals to 1,1,1-trichloroethane.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to 1,1,1-trichloroethane.

Only one oral study investigated the respiratory effects of 1,1,1-trichloroethane in animals. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day by gavage did not affect the incidence of lesions in the lungs, trachea, or nasal passages (NCI 1977). NOAEL values derived from this study are recorded in Table 3-2 and plotted in Figure 3-2. Based on the negative results in the NCI (1977) study and the generally negative results in inhalation studies in which respiratory tissues came into direct contact with high levels (see Section 3.2.1.2), 1,1,1-trichloroethane is not expected to produce respiratory effects following ingestion in humans.

Cardiovascular Effects. Electrocardiogram readings were normal 4 hours after a man accidentally drank a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966).

Cardiovascular effects of ingested 1,1,1-trichloroethane have been investigated only by histopathological examination of exposed animals. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day did not affect the incidence of lesions in the heart (NCI 1977). NOAEL values derived from this study are recorded in Table 3-2 and plotted in Figure 3-2.

The usefulness of histopathological heart examinations is limited, considering the findings of serious effects on cardiovascular function without pathological lesions in animals after acute exposure to high

levels of 1,1,1-trichloroethane via inhalation. Therefore, existing data are insufficient to assess cardiovascular effects from oral exposure to 1,1,1-trichloroethane.

Gastrointestinal Effects. Severe vomiting and diarrhea began 1 hour after ingestion and continued for 6 hours in a man who survived after accidentally drinking a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966). The patient reported feeling a burning sensation in his mouth and throat immediately after swallowing the dose.

Gastrointestinal effects of orally administered 1,1,1-trichloroethane were investigated only by histopathological examination in animals. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day by gavage in oil did not affect the incidence of nonneoplastic lesions in the stomach, intestines, and pancreas (NCI 1977). NOAEL values derived from this study are recorded in Table 3-2 and plotted in Figure 3-2.

The results of the NCI (1977) study suggest that 1,1,1-trichloroethane does not produce gastrointestinal toxicity, while the case report of Stewart and Andrews (1966) shows that swallowing a large, undiluted dose of this chemical can produce severe gastrointestinal upset and some irritation of the throat.

Hematological Effects. Hematological parameters remained within normal limits in tests beginning 4 hours after exposure in a man who survived after accidentally drinking a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966).

Oral exposure of rats and mice to 1,1,1-trichloroethane in the diet at concentrations as high as 80,000 ppm (approximate doses as high as 5,000 and 23,000 mg/kg/day in rats and mice, respectively) did not result in apparent treatment-related hematological effects (NTP 2000). Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day by gavage in oil did not affect the incidence of nonneoplastic lesions in the bone marrow (NCI 1977). NOAEL values derived from this study are recorded in Table 3-2 and plotted in Figure 3-2.

The limited data available suggest that ingested 1,1,1-trichloroethane does not produce hematological effects.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to 1,1,1-trichloroethane.

Only one study investigated musculoskeletal effects in animals exposed to 1,1,1-trichloroethane orally. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day by gavage in oil did not affect the incidence of nonneoplastic lesions in the muscles or bones (NCI 1977). NOAEL values derived from this study are recorded in Table 3-2 and plotted in Figure 3-2.

Hepatic Effects. Stewart and Andrews (1966) reported a case in which a man survived drinking 1 ounce (600 mg/kg) of 1,1,1-trichloroethane. Serum transaminase levels remained within normal limits, but serum bilirubin levels became slightly elevated after 48 hours. Increased serum bilirubin levels may result from reduced biliary excretion (i.e., cholestatic liver damage). Alternatively, hyperbilirubinemia may result from diminished hepatic conjugative metabolism of bilirubin.

Elevated SGOT levels, often seen in conjunction with hepatic damage and damage of other tissues, were reported in rats given a single oral dose of 1,330 mg/kg 1,1,1-trichloroethane (Tyson et al. 1983). Levels of SGPT, which is more specific for liver damage, remained unchanged in this study, however. Similar results in rats (little change in SGPT activity) were reported by others (Xia and Yu 1992). There were no indications of 1,1,1-trichloroethane-induced liver damage in rats given a single gavage dose of 4,000 mg/kg/day or repeated gavage doses as high as 10,000 mg/kg/day (Bruckner et al. 2001). Data regarding the effect of 1,1,1-trichloroethane on the activity of rat liver enzymes are inconclusive. Increased liver microsomal and cytoplasmic protein content were found, although they were not accompanied by increases in activity of enzymes or increased liver weight (Platt and Cockrill 1969). Reduced levels of cytochrome P-450 and epoxide hydratase, suggesting inhibition of these enzymes, was reported in another study (Vainio et al. 1976). Bruckner et al. (2001) found some evidence in rats of enzyme induction at low doses and inhibition at high doses. In an intermediate-duration study, mild liver effects (small increases in SGPT and ornithine carbamyl transferase [OCT]) occurred at 5,000 mg/kg/day (Bruckner et al. 2001). Relative liver weight was increased by approximately 11% ($p<0.05$) in rats administered 1,1,1-trichloroethane by oral gavage for 21 days, but there were no histopathological signs of hepatotoxicity (NTP 1996). Decreased liver weights in female rats administered 80,000 ppm (5,000 mg/kg/day) of 1,1,1-trichloroethane in the diet for 13 weeks were attributed to reduced body weights, not adverse liver effects (NTP 2000). No liver effects were seen in similarly treated male rats, or in male or female mice receiving doses as high as 15,000 and 23,000 mg/kg/day, respectively. Chronic

gavage administration of 1,1,1-trichloroethane did not affect the incidence of nonneoplastic lesions in the livers of rats or mice (NCI 1977). The highest NOAEL values and all reliable LOAEL values for hepatic effects in each species and exposure duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Human and animal studies suggest that large amounts of ingested 1,1,1-trichloroethane may produce mild hepatotoxicity; however, whether 1,1,1-trichloroethane is an inducer or inhibitor of biotransformation enzymes following oral exposure is unclear.

Renal Effects. BUN levels were not elevated 4 hours after a man accidentally ingested a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966).

No effects on kidney weight or histology were found in rats given a single gavage dose of 4,000 mg/kg/day, repeated doses of 10,000 mg/kg/day, or intermediate-duration exposure to 5,000 mg/kg/day (Bruckner et al. 2001). There was a slight transient increase in BUN in the rats repeatedly given 10,000 mg/kg/day (Bruckner et al. 2001). Urinalysis performed on male rats administered 165 mg/kg/day of 1,1,1-trichloroethane by gavage for 21 days revealed significant increases in mean urinary protein and SGOT, but no histopathological evidence of renal damage (NTP 1996). The statistical significance of this finding is questionable since it was based on only four surviving rats. Male rats administered ≥10,000 ppm (600 mg/kg/day) of 1,1,1-trichloroethane in the diet for 13 weeks exhibited kidney lesions indicative of hyaline droplet nephropathy (NTP 2000); this effect is specific to male rats and is not a human health concern. Chronic gavage exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day did not affect the incidence of nonneoplastic lesions in the kidneys (NCI 1977). NOAEL values derived from these studies are recorded in Table 3-2 and plotted in Figure 3-2.

Data from animals suggest that the kidney is not a target of 1,1,1-trichloroethane taken orally. Sensitive tests of renal function have not apparently been performed, however, in animals ingesting 1,1,1-trichloroethane.

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to 1,1,1-trichloroethane.

Only one study investigated dermal effects following oral exposure in animals. Chronic oral exposure by gavage of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day of 1,1,1-trichloroethane did not affect the

incidence of nonneoplastic skin lesions (NCI 1977). NOAEL values derived from this study are recorded in Table 3-2 and plotted in Figure 3-2. The scarcity of data regarding dermal effects in humans or animals after oral exposure to 1,1,1-trichloroethane precludes assessing potential injury of this tissue.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to 1,1,1-trichloroethane.

Several studies monitored body weight in animals dosed orally with 1,1,1-trichloroethane. Reduced body weight gain was produced in rats by repeated doses ≥5,000 mg/kg/day in short-term studies and ≥2,500 mg/kg/day in intermediate-duration studies (Bruckner et al. 2001). Reduced body weight gain was noted in male (but not female) rats administered 1,1,1-trichloroethane in the diet at a concentration of 80,000 ppm (doses as high as 4,800 and 5,000 mg/kg/day in males and females, respectively) for 13 weeks (NTP 2000). In similarly treated male and female mice, reduced body weight gain was observed at 1,1,1-trichloroethane concentrations ≥5,000 and 10,000 ppm, respectively (doses of approximately 850 and 2,850 mg/kg/day, respectively) (NTP 2000). An intermediate-duration oral MRL of 18 mg/kg/day was derived for 1,1,1-trichloroethane based on the results of this study, as described in the footnote in Table 3-2. In another study, reduced body weight gain was reported at 5,620 mg/kg/day in rats exposed for 6 weeks and 750 mg/kg/day in rats exposed for 78 weeks (NCI 1977). Body weight gain in rats was reduced by an even lower dose (500 mg/kg/day) in a second chronic study, but only after 80 weeks of exposure (Maltoni et al. 1986). In mice, 5,620 mg/kg/day did not affect body weight in a 6-week study, but 2,807 mg/kg/day was sufficient to reduce body weight gain in a 78-week study (NCI 1977). These limited data on the effects of orally administered 1,1,1-trichloroethane on body weight gain in animals suggest time- and dose-response relationships.

The highest NOAEL values and all reliable LOAEL values for body weight effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to 1,1,1-trichloroethane.

Immunological effects in animals were investigated only by histopathological examination of certain tissues. There was no effect on the incidence or type of nonneoplastic lesions in the thymus or spleen of rats or mice after chronic gavage exposure to high doses of 1,1,1-trichloroethane (NCI 1977). NOAEL values derived from this study are recorded in Table 3-2 and plotted in Figure 3-2. The scarcity of data pertaining to immunological effects in humans or animals after oral exposure to 1,1,1-trichloroethane precludes an assessment of immunotoxicity.

3.2.2.4 Neurological Effects

A thorough neurological examination (details not reported) found no abnormalities in a man who had ingested 600 mg/kg of 1,1,1-trichloroethane 4 hours earlier (Stewart and Andrews 1966).

Acute oral exposure of rats to 1,1,1-trichloroethane (705 mg/kg/day) did not result in behavior or appearance changes that could be detected after 2 days by a battery of observational measures, but did produce distinct neurophysiological alterations after 4 days. These alterations included marked changes in the flash-evoked potential (FEP) and electroencephalogram (EEG) recordings. Such effects are similar to those seen after inhalation exposure, and smaller changes in the somatosensory-evoked potential (SEP) (Spencer et al. 1990). No significant changes in tissue levels of monoamine neurotransmitters and metabolites were found in the brain of rats given single oral doses of 3,250 mg/kg of 1,1,1-trichloroethane and sacrificed 2 hours later (Kanada et al. 1994). Rats given high oral doses of 1,1,1-trichloroethane (≥2,500 mg/kg/day) exhibited a short period of hyperactivity, followed by a period of prolonged narcosis after daily dosing in acute- and intermediate-duration studies (Bruckner et al. 2001). No clinical signs of neurotoxicity were seen in rats and mice receiving 1,1,1-trichloroethane in the diet at concentrations as high as 80,000 ppm (doses as high as 4,800 and 5,000 mg/kg/day in males and females, respectively) for 13 weeks (NTP 2000). Neurological effects were investigated by histopathological examination of the brain and nerves in a chronic study (NCI 1977). There was no effect on the incidence or type of lesions in the brain or nerves of rats or mice after chronic gavage exposure to 1,1,1-trichloroethane (NCI 1977). Failure to detect neural lesions by routine histopathology in this study does not rule out the occurrence of neurological effects following chronic oral exposure since physical changes in the brain did not accompany residual neurological effects seen in inhalation studies.

Reliable NOAEL and LOAEL values for neurological effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2. Limited information is available regarding the neurological effects of 1,1,1-trichloroethane following oral exposure, but the observation of narcosis in the studies by Bruckner et al. (2001) and the results of the acute neurophysiology study in rats suggest that the neurotoxicity of orally administered 1,1,1-trichloroethane may be similar to that observed following inhalation exposure.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to 1,1,1-trichloroethane.

Limited information is available regarding reproductive effects in animals following oral exposure to 1,1,1-trichloroethane. A multigeneration reproduction study was conducted in mice by Lane et al. (1982). Male and female mice were exposed to 1,1,1-trichloroethane (1,000 mg/kg/day) in their drinking water. In the parental and F1 generations, exposure began prior to mating and was continued through gestation and lactation. Exposure usually precedes mating by the length of the sperm cycle in studies of this type, but the duration of premating exposure for the parental generation was abbreviated in this study. Treatment did not affect maternal survival, body weight, or reproductive performance. In another study, rats were exposed to up to 3 mg 1,1,1-trichloroethane/kg/day in the drinking water from before mating through lactation (George et al. 1989; NTP 1988a). Maternal survival, body weight, fertility, and the duration of gestation were not affected. Reduced epididymal spermatozoal concentration was noted male rats and mice administered 1,1,1-trichloroethane in the diet at a concentration of 80,000 ppm (approximate doses of 4,800 and 15,000 mg/kg/day) for 13 weeks, but there were no other indications of adverse male reproductive effects and no signs of altered estrus in similarly-treated female rats and mice (NTP 2000). In a chronic-duration study in rats and mice, there was no effect on the incidence or type of nonneoplastic lesions in the prostate, seminal vesicles, testes, or epididymis in males, or the uterus or ovary in females (NCI 1977).

The highest NOAEL values for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2. There is limited evidence that oral exposure to high doses of 1,1,1-trichloroethane may influence sperm production in animals.

3.2.2.6 Developmental Effects

The possible relationship between developmental effects and exposure to 1,1,1-trichloroethane in the drinking water was investigated in a series of epidemiology studies (Deane et al. 1989; Wrensch et al. 1990a; 1990b). A leak in an underground storage tank resulted in contamination of well water with 1,1,1-trichloroethane and other chemicals. Levels of 1,1,1-trichloroethane were far higher than levels of other chemicals (1,700 ppb when first detected, reaching a maximum of 8,800 ppb after the well was closed). An excess of miscarriages and birth defects occurred in one exposed community but not in another. Hydrogeological modeling of water and contaminant distribution within the exposed communities showed that the leak was probably not responsible for the excessive adverse pregnancy outcomes in the one community, because estimated exposure to 1,1,1-trichloroethane was lower than in the other community. Average estimated exposure, in fact, was lower in areas reporting births with malformations than in those without. A related study, conducted on a larger scale, found an excess of major cardiac anomalies during the exposure period in the service area of the water company with the contaminated well, compared to the rest of the county (Santa Clara, California) (Swan et al. 1989). no file Detailed analysis of the temporal and spatial distribution of cases, however, did not support the hypothesis that contamination of the well produced these adverse effects. In a more recent report, no statistically significant effects were seen in a 3-year assessment of birth outcome among northern New Jersey residents of 75 towns where some water supplies were contaminated with 1,1,1-trichloroethane and other chemicals (Bove et al. 1995).

Lane et al. (1982) investigated the developmental effects of 1,1,1-trichloroethane in mice in a multigeneration reproduction study modified to allow screening for teratogenic and dominant lethal effects. Mice of either sex were exposed to 1,1,1-trichloroethane in their drinking water. Exposure for the initial test mice and the subsequent F1 generation began before mating and continued throughout gestation and lactation. Exposure is usually intended to precede mating by the length of the sperm cycle; however, in this study, the duration of premating exposure for the parental generation was abbreviated. No maternal toxicity was reported. There were no treatment-related embryotoxic or fetotoxic effects in either the F1 or F2 generation. Pup survival and body weight were also unaffected. There was no increase in the frequency of dominant lethal factors or in the incidence of skeletal or visceral malformations in either generation.

No file

The developmental effects of 1,1,1-trichloroethane were also studied in rats (George et al. 1989; NTP 1988a, 1988b). Doses of up to 3 mg/kg/day of the chemical were administered in these studies to allow comparison with preliminary results of an earlier study (Dapson et al. 1984; Hutcheon et al. 1985) that reported increased incidences of cardiovascular anomalies at these doses. In the first study (NTP 1988a), 1,1,1-trichloroethane was added to the drinking water of male and female rats before mating and through lactation. Exposure to 1,1,1-trichloroethane had no effect on pup survival or body weight, or on the incidence of malformed pups. Particular attention was paid to developmental effects on the cardiovascular system. There was a high incidence of patent ductus arteriosus among pups that died on postnatal day 1 (10/28 exposed versus 0/8 control). Patent ductus arteriosus was found in only one treated pup (from the low-concentration group) sacrificed on postnatal day 4. No cardiovascular anomalies of any type were found in treated pups sacrificed on postnatal day 21, which was the time that Dapson et al. (1984) reported effects. The authors explain that patent ductus arteriosus is not unexpected in pups at the earlier time points (days 1 and 4), but do not address the apparent difference between treated and control groups on day 1. Most of the pups with patent ductus arteriosus were in the low-dose group; incidence was lower in the two higher-dose groups, and the effects were not statistically significant. These results suggest that 1,1,1-trichloroethane did not affect the development of patent ductus arteriosus in these rats.

No file

In the second study (NTP 1988b), rats were exposed to up to 2.5 mg/kg/day in the drinking water from premating through gestation. Dams were sacrificed on day 20 of gestation, and the fetuses were given comprehensive teratological examinations. No embryotoxic or fetotoxic effects were reported. There was no effect on the incidence of external, visceral, or skeletal malformations. No cardiovascular abnormalities of any type were seen.

A study was designed to examine the neurobehavioral effects of 1,1,1-trichloroethane on the offspring of rats treated with the test material by gavage on gestation day 6 through lactation day 10 (Dow Chemical 1993; Maurissen et al. 1994). The doses used were 75, 250, and 750 mg 1,1,1-trichloroethane/kg/day. The end points examined included body weight, physical maturation landmarks, motor activity, functional observation battery, brain measurements and neuropathology, and evaluation of learning capacity, task performance, and short-term memory. Although sporadic differences between treated animals and controls were found with some tests, these were either not statistically significant or not dose-related, suggesting that the highest dose tested, 750 mg/kg/day, was a NOAEL for the study.

The highest NOAEL values for developmental effects in each species are recorded in Table 3-2 and plotted in Figure 3-2. The weight of evidence in experimental animal studies suggests that 1,1,1-trichloroethane is not a developmental toxicant when administered orally; however, this conclusion is limited by the use of low doses in some of the studies. Epidemiology studies found no evidence that exposure to 1,1,1-trichloroethane was responsible for the cluster of adverse pregnancy outcomes in Santa Clara County, California.

3.2.2.7 Cancer

Isacson et al. (1985) investigated the relationship between the presence of organic chemicals, including 1,1,1-trichloroethane, in drinking water and the incidence of cancer in Iowa residents. The authors contrasted towns that had detectable quantities of 1,1,1-trichloroethane in the water supply with those that did not and found no difference in the incidence of bladder, colon, lung, rectum, breast, or prostate cancer in people over age 55. 1,1,1-Trichloroethane levels >0.1 μg/L (but unspecified) were detectable in this study. Assuming the average adult weighs 70 kg and drinks 2 liters of water per day, a concentration of 0.1 μg/L would produce a dose of approximately 0.000003 mg/kg/day. The authors concede that their data are not sensitive enough to support conclusions regarding the apparent lack of association between 1,1,1-trichloroethane in the water supply and cancer risk in humans. No other studies were located regarding risks of cancer in humans after oral exposure to 1,1,1-trichloroethane.

NCI (1977) conducted a bioassay for carcinogenicity of 1,1,1-trichloroethane in rats and mice. The test animals were exposed to high gavage doses of the chemical (750 or 1,500 mg/kg/day for rats and 2,807 or 5,615 mg/kg/day for mice) for 78 weeks. All animals were necropsied and the tissues were examined histologically. The incidence and type of neoplasms observed were similar to those seen in untreated controls. Vehicle controls were not used in this study. There was a significant dose-related decrease in survival of both rats and mice. Among rats, no males and only 2–4% females survived to the end of the experiment. Among mice, 22–30% of treated males and 26–46% of treated females survived. Because the high rate of early mortality may have lowered the incidence of late-appearing tumors, the authors did not consider this study an adequate test of 1,1,1-trichloroethane carcinogenicity in either species.

A screening-type study using only one gavage dose level (500 mg/kg/day for 104 weeks) and a less-than-optimal sample size (40 per sex) reported an apparent increase in leukemia incidence in rats (Maltoni et al. 1986). Survival appeared comparable between control and treatment groups, but no statistical analysis was performed. Body weight was reduced in females after 80 weeks of the experiment. Although tumor incidences were not analyzed statistically, an apparent increase in the total incidence of leukemias occurred, with 13 in treated rats and 4 in vehicle controls. The increase was due mainly to an increased incidence of immunoblastic lymphosarcomas in the lungs (seven in treated rats and one in controls). The biological and statistical significance of this finding cannot be determined because of the inherent limitations of the experimental design. The authors stated that, although definite conclusions could not be drawn based on this study, the results called for further experimentation to assess the carcinogenicity of 1,1,1-trichloroethane.

The inability to identify associations between human oral exposure and cancer incidence, as well as the limitations of the animal studies (i.e., high rate of early mortality, one dose level, small sample size), limit the assessment of potential carcinogenic effects in humans after oral exposure to 1,1,1-trichloroethane.

3.2.3 Dermal Exposure

Occupational exposure to 1,1,1-trichloroethane frequently involves both inhalation of and dermal contact with the chemical. There are many case reports of effects in individuals after occupational exposure to high levels of 1,1,1-trichloroethane, but inhalation appears to be the primary route of exposure in most such cases. Although dermal exposure may have contributed to the effects observed, these cases are discussed under Inhalation Exposure in Section 3.2.1. In a few cases, dermal exposure appeared to be more important, and these are discussed below. In all cases, except for superficial skin effects, any potential effect would likely be similar to inhalation effects at similar circulating blood levels.

3.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to 1,1,1-trichloroethane.

Very high dose levels were required to cause death in animals after dermal exposure to 1,1,1-trichloroethane. Exposure to 15,800 mg/kg under a cuff killed <50% of the rabbits tested (Torkelson et al. 1958).

Acute dermal exposure to lower doses did not cause death in rabbits or guinea pigs (Kinkead and Leahy 1987; Torkelson et al. 1958; Wahlberg and Boman 1979). Repeated-exposure studies employing doses up to 280 mg/kg/day (covered) or 500 mg/kg/day (uncovered) did not reveal any effect on mortality in rats or rabbits (Torkelson et al. 1958; Viola et al. 1981).

These limited data suggest that dermal exposure to 1,1,1-trichloroethane is lethal only at very high doses that could not be experienced under foreseeable circumstances. The LOAEL for death in acutely exposed rabbits is recorded in Table 3-3.

3.2.3.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration are recorded in Table 3-3.

No reports were located in which musculoskeletal, endocrine, or metabolic effects were associated with oral exposure of humans or animals to 1,1,1-trichloroethane.

Respiratory Effects. No studies were located regarding respiratory effects in humans after dermal exposure to 1,1,1-trichloroethane.

Respiratory effects in animals were investigated by pathological examination of the lungs in one study. Dermal exposure for 90 days to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) had no effect on lung weight or the incidence of gross or microscopic lung lesions in rabbits (Torkelson et al. 1958). A NOAEL derived from this study is recorded in Table 3-3.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after dermal exposure to 1,1,1-trichloroethane.

Cardiovascular effects in animals were investigated by histopathological examination in one study. Intermittent 90-day dermal exposure to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) had no effect on heart weight or the incidence of heart lesions in rabbits (Torkelson et al. 1958). A NOAEL derived from this study is recorded in Table 3-3. Much higher doses may be required to produce effects by the

dermal route; high vapor concentrations were required to produce cardiotoxic effects by inhalation exposure, and percutaneous absorption of 1,1,1-trichloroethane is much slower and less complete than pulmonary absorption.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after dermal exposure to 1,1,1-trichloroethane.

Gastrointestinal effects were not seen in animals dermally exposed to 1,1,1-trichloroethane. Rats exposed to 280 mg/kg/day of 1,1,1-trichloroethane under an occlusive dressing for 3 weeks showed no evidence of pancreatic damage, as determined by histopathological examination and serum lipase and amylase levels (Viola et al. 1981). Rabbits exposed to 500 mg/kg/day without occlusion for 90 days had no gross or microscopic lesions in the stomach or intestines (Torkelson et al. 1958).

These limited animal data suggest that dermal exposure to 1,1,1-trichloroethane will not result in gastrointestinal effects in humans. The NOAEL values for gastrointestinal effects in rats and rabbits are recorded in Table 3-3.

Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to 1,1,1-trichloroethane.

One study of hematological effects in dermally-exposed animals was located. Hematological parameters, including red blood cell count, white blood cell count, and hemoglobin, were unaffected by dermal exposure to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) for 90 days in rabbits (Torkelson et al. 1958). A NOAEL derived from this study is recorded in Table 3-3. The scarcity of human and animal data limits the assessment of hematological effects that may be caused by dermal exposure to 1,1,1-trichloroethane.

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to 1,1,1-trichloroethane.

Mild hepatic effects have been reported in animals after dermal exposure to 1,1,1-trichloroethane. Levels of SGOT, ornithine carbamyl transferase, and gamma-glutamyl transferase, enzymes released into the serum from damaged hepatocytes, were significantly increased in rats dermally exposed to 280 mg/kg/day

of 1,1,1-trichloroethane under occlusion in a 3-week study (Viola et al. 1981). Levels of SGPT, another indicator of hepatic damage, were not affected. Histopathological effects, including damage to hepatocytes (fatty degeneration and mitochondrial swelling) and the presence of small focal intralobular inflammatory infiltrates, were seen in the exposed rats. A study in which rabbits were dermally exposed to higher doses of 1,1,1-trichloroethane for a longer period (but without occlusion) did not reveal histopathological effects in the liver or changes in liver weight (Torkelson et al. 1958).

Animal data suggest that dermal exposure to high doses of 1,1,1-trichloroethane may result in liver effects. Although too little information exists to allow a detailed evaluation, skin absorption is not likely to be a problem for foreseeable exposures. The NOAEL and LOAEL values for hepatic effects are recorded in Table 3-3.

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to 1,1,1-trichloroethane.

Renal effects were investigated in two animal studies. Histopathological examination of the kidneys found no lesions following repeated dermal exposure to 280 mg/kg/day (covered) in rats or 500 mg/kg/day (uncovered) in rabbits (Torkelson et al. 1958; Viola et al. 1981).

The scarcity of human and animal data limits the assessment of renal effects that may be caused by dermal exposure to 1,1,1-trichloroethane. The NOAEL values for renal effects in rats and rabbits are recorded in Table 3-3.

Dermal Effects. Dermal exposure to 1,1,1-trichloroethane causes reversible effects in humans, which increase from mild irritation to chemical burns as exposure duration increases. Volunteers who immersed their thumbs in beakers of undiluted 1,1,1-trichloroethane for 30 minutes reported mild burning pain after ≈10 minutes of exposure (Stewart and Dodd 1964). Following exposure, mild erythema and fine scaling were visible on the thumb. The scaling was easily rinsed and the erythema disappeared within 1 hour. Similar results were obtained when the entire hand was immersed in the beaker, except that the burning sensation began earlier, became more intense, and then was replaced by a feeling of cold that continued 10 minutes after exposure ended. When the subject repeatedly alternated immersion in 1,1,1-trichloroethane with exposure to air, intense cold was produced by evaporation of 1,1,1-trichloroethane from the skin. The hand remained cold for 45 minutes after the end of exposure.

Brief dermal exposure to a small amount of 1,1,1-trichloroethane covered with a glass disk produced an immediate increase in blood flow that dropped back to pre-exposure levels after 1 hour (Wahlberg 1984a). Slight, transient erythema was visible from 10 to 20 minutes following exposure. The subject reported mild stinging and burning sensations. None of these effects were found when a smaller amount of 1,1,1-trichloroethane was allowed to spread freely on the subject's skin, probably due to rapid evaporation of the chemical (Wahlberg 1984a). Repeated uncovered application of a small amount had no effect on skin-fold thickness and produced no visible dermal reaction (Wahlberg 1984b).

One case of allergic contact dermatitis from 1,1,1-trichloroethane was located in the literature (Ingber 1991). A worker whose job included using 1,1,1-trichloroethane to clean metal plates developed severe acute hand eczema soon after starting the job. The eczema persisted throughout 3 years of employment. Patch tests at that time showed a positive reaction to 1,1,1-trichloroethane. The eczema disappeared after a few weeks when contact with 1,1,1-trichloroethane was avoided. The possibility of the allergic reaction to being caused by 1,1,1-trichloroethane stabilizer was not discussed. (Very rare response to TCE exposure)

file hard to read

Assessments of the skin irritancy of 1,1,1-trichloroethane in animals reveal slight to moderate reactions. Based on single-application studies in rabbits, 1,1,1-trichloroethane was ranked as a moderate skin irritant by Duprat et al. (1976). A single application of 1,1,1-trichloroethane to the mouse ear resulted in significantly increased ear thickness approximately 1 hour following treatment (Iyadomi et al. 2000). Torkelson et al. (1958), however, reported only slight reddening and scaliness of rabbits' skin following a single application. Irritation observed following repeated application of the compound for 10 days was only slightly more noticeable and quickly disappeared after the end of treatment (Torkelson et al. 1958). Skin-fold thickness increased 41–81% in rabbits and guinea pigs exposed repeatedly to dermal applications of 1,1,1-trichloroethane, and visible erythema and edema were present within 24–72 hours of the original exposure (Wahlberg 1984b). Intermediate-duration exposure to doses ranging from 15 to 500 mg/kg/day produced only slight, reversible irritation at the application site (Torkelson et al. 1958). Lack of dose and exposure methodology information makes it difficult to compare the results of these studies, but the weight of evidence suggests that 1,1,1-trichloroethane is not a strong dermal irritant in animals.

not as potent as other cmpds.

Kronevi et al. (1981) studied cellular changes produced in the intact skin of guinea pigs by exposure to 1 mL of undiluted 1,1,1-trichloroethane under a cover glass for durations ranging from 15 minutes to

16 hours. No gross effects were observed, indicating that the overall irritation produced was minor, but a host of degenerative changes in the epidermis, including karyopyknosis, karyolysis, perinuclear edema, and spongiosis, was found by histological examination. Focal junctional separation and cellular infiltration were observed in the upper part of the dermis. Effects were seen within 15 minutes of exposure, and some were still evident 16 hours later.

Exposure to 4,000 ppm 1,1,1-trichloroethane in the air for 4 hours caused the fur coat of mice to become dull (Evans and Balster 1993). This effect was most likely caused by direct contact of the chemical with the skin (see also Section 3.2.1.2).

Although extended dermal contact with relatively concentrated 1,1,1-trichloroethane may cause irritation and burning sensations of the skin of humans, most evidence in humans and animals indicates that this compound is not a strong skin irritant. There is one report of a 1,1,1-trichloroethane formulation acting as a skin sensitizer in humans. The highest NOAEL values and all reliable LOAEL values for dermal effects in each species and duration category are recorded in Table 3-3.

Ocular Effects. Individuals briefly exposed to high 1,1,1-trichloroethane vapor concentrations reported mild eye irritation (Stewart et al. 1961). This effect was most likely due to direct contact of the chemical with the eye.

Ocular administration of 1,1,1-trichloroethane caused only mild eye irritation in rabbits (Duprat et al. 1976; Krantz et al. 1959; Marzulli and Ruggles 1973; Torkelson et al. 1958). The study by Marzulli and Ruggles (1973) was a survey in which 10 laboratories conducted the Draize eye test in rabbits using 1,1,1-trichloroethane and reported little or no eye irritation.

Although eye irritation produced by direct application of 1,1,1-trichloroethane seems to be minor, mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane in the air for 4 hours exhibited eye irritation during exposure (Evans and Balster 1993). The highest NOAEL values and all reliable LOAEL values for ocular effects in each species and duration category are recorded in Table 3-3.

Body Weight Effects. No studies were located regarding body weight effects in humans after dermal exposure to 1,1,1-trichloroethane.

Animal studies have investigated the effect of topical 1,1,1-trichloroethane application on body weight. Acute exposure to 7,360 mg/kg of 1,1,1-trichloroethane (covered) decreased body weight gain in guinea pigs (Wahlberg and Boman 1979). A lower dose had no effect on body weight in rabbits (Kinkead and Leahy 1987). Intermediate exposure to 280 mg/kg/day under occlusion reduced growth in rats (Viola et al. 1981). Exposure to a higher dose for a longer period did not affect rabbit body growth, but 1,1,1-trichloroethane was applied uncovered in this study (Torkelson et al. 1958). Food consumption was not monitored in these studies. Effects of 1,1,1-trichloroethane on body weight may have been produced by effects on appetite and food intake secondary to central nervous system depression, rather than physiological effects on growth and development.

The scarcity of human and animal data limits the assessment of body weight effects caused by dermal exposure to 1,1,1-trichloroethane. The NOAEL and LOAEL values for body weight changes are recorded in Table 3-3.

3.2.3.3 Immunological and Lymphoreticular Effects

One report of a worker who developed allergic contact dermatitis to a formulation of 1,1,1-trichloroethane (Ingber 1991) is discussed in more detail under Dermal Effects in Section 3.2.3.2.

In animals, immunological effects following dermal exposure were investigated only by histopathological examination. No lesions or weight changes were found in the spleens of rabbits exposed to moderate 1,1,1-trichloroethane levels (500 mg/kg/day; no occlusion) in a 90-day study (Torkelson et al. 1958). The NOAEL value derived from this study is recorded in Table 3-3. The scarcity of human and animal data precludes the assessment of potential effects on immune system tissues and function after dermal exposure to 1,1,1-trichloroethane.

3.2.3.4 Neurological Effects

Three women developed peripheral neuropathy after frequent, prolonged dermal contact with formulations of 1,1,1-trichloroethane and other chemicals at their workplace (Howse et al. 1989; Liss 1988). The women initially complained of numbness in their limbs, and subsequent nerve conduction studies showed alterations in peripheral nerve activity. The effect was diagnosed as primarily a distal

sensory peripheral neuropathy. These cases were unusual because the effect was greater in the hands than in the feet, the reverse of most peripheral neuropathies. Sural nerve biopsies in two of the women performed 3–4 years after diagnosis revealed chronic neuropathy (axonopathy and myelinopathy) (Liss 1988). The authors did not establish a causal relationship with 1,1,1-trichloroethane. Two more recent cases of peripheral neuropathy were reported following exposure to 1,1,1-trichloroethane used as a degreasing agent (House et al. 1994, 1996).

Dermal studies including tests of neurological function in animals were not located. Neurological effects were investigated by histopathological examination of the brain in one study. The value of these data is limited, however, since physical changes in the brain have not been found to accompany serious neurological effects in high level inhalation studies. No lesions or weight changes were found in the brains of rabbits exposed to 500 mg/kg/day of 1,1,1-trichloroethane (no occlusion) in a study of intermediate duration (Torkelson et al. 1958). The NOAEL value derived from this study is recorded in Table 3-3. These data are not sufficient for assessing the neurotoxicity of 1,1,1-trichloroethane after dermal exposure to the compound.

3.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after dermal exposure to 1,1,1-trichloroethane.

Reproductive effects following dermal exposure were investigated only by histopathological examination in animals. No lesions or weight changes were found in the testes of rabbits exposed to 500 mg/kg/day of 1,1,1-trichloroethane (no occlusion) in a study of intermediate duration (Torkelson et al. 1958). The NOAEL value derived from this study is recorded in Table 3-3. The absence of human data, tests in female laboratory animals, and evaluation of reproductive function prevents an acceptable assessment of possible reproductive effects from dermally administered 1,1,1-trichloroethane.

3.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after dermal exposure to 1,1,1-trichloroethane.

3.2.3.7 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to 1,1,1-trichloroethane.

3.3 GENOTOXICITY

The genotoxic effects of 1,1,1-trichloroethane have been studied extensively. The results are summarized in Tables 3-4 and 3-5. Although most tests of mutagenicity in the Ames *Salmonella* assay produced negative results, those conducted in a desiccator, to minimize evaporation and maximize exposure, were mostly positive (Gocke et al. 1981; Nestmann et al. 1980, 1984; Simmon et al. 1977). These results indicate that 1,1,1-trichloroethane may be mutagenic in *Salmonella*. The results were negative in other tests of genotoxicity in bacteria and fungi. 1,1,1-Trichloroethane is a relatively volatile compound; therefore, a high evaporation rate could result in lower doses reaching the microorganisms and thus affect the outcome of genotoxicity tests. This explanation may account for the largely negative results observed in tests with bacteria and fungi. On the other hand, many compounds more volatile than 1,1,1-trichloroethane are positive in these studies. A weakly positive result was obtained in a test for induction of deletions via intrachromosomal recombination in the yeast *Saccharomyces cerevisiae* (Brennan and Schiestl 1998).

Most assays of genotoxicity in mammalian cells have been negative, but 1,1,1-trichloroethane did produce chromosomal aberrations in Chinese hamster ovary cells *in vitro* (Galloway et al. 1987). *In vivo* micronucleus tests for chromosomal aberrations were all negative (Gocke et al. 1981; Katz et al. 1981; Halogenated Solvents Industry Alliance 1990; Salamone et al. 1981; Tsuchimoto and Matter 1981). Positive or weakly positive results were reported in assays for unscheduled DNA synthesis in mouse hepatocytes (Milman et al. 1988); degranulation of endoplasmic reticulum, which measures the ability of a compound to displace polysomes from endoplasmic reticulum in rat hepatocytes *in vitro* (Fey et al. 1981); and formation of DNA adducts (binding of the compound to DNA) in mouse liver *in vivo* (Turina et al. 1986). Tests of cell transformation in rat embryo cells, hamster embryo cells, baby hamster kidney cells, and mouse BALB/c-3T3 cells were almost all positive (Daniel and Dehnel 1981; Hatch et al. 1982;

1983; Milman et al. 1988; Price et al. 1978; Tu et al. 1985). Cell transformation systems are believed to be similar to the process of neoplastic transformation. in vivo. (depends upon what you measure).

Although 1,1,1-trichloroethane was mutagenic in a few assays with *Salmonella*, induced chromosomal aberrations in a Chinese hamster ovary cell assay, and was positive in most mammalian cell transformation assays, the existing genotoxicity data are largely negative. In addition, positive results may have been produced by stabilizers and not 1,1,1-trichloroethane itself. Therefore, a firm conclusion regarding the genotoxic potential of 1,1,1-trichloroethane in humans is not possible.

3.4 TOXICOKINETICS

Upon first exposure, 1,1,1-trichloroethane is rapidly and efficiently absorbed by the lung, skin (under conditions to prevent evaporation), and gastrointestinal tract of humans and animals. As the duration of inhalation exposure increases, the percentage of absorption decreases because steady-state levels are approached in the blood and tissues, and 1,1,1-trichloroethane is metabolized at a low rate. Animal studies have demonstrated that, once absorbed, 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, including to developing fetuses, with preferential distribution to fatty tissues. The predominant pathway of elimination of 1,1,1-trichloroethane in humans and animals, regardless of route of exposure, is exhalation of the unchanged compound. When exposure ceases, the compound is rapidly cleared from the body. In animal studies, only trace amounts of the compound remain in tissues within days of the termination of short-term exposure.

1,1,1-Trichloroethane is metabolized oxidatively, at low rates, to trichloroethanol and trichloroacetic acid by the cytochrome P-450 mixed-function oxidase system. These metabolites are excreted in the urine; other minor metabolites (carbon dioxide [CO_2] and acetylene) are excreted in expired air. (The acetylene is formed by reductive dechlorination of 1,1,1-trichloroethane under conditions of low oxygen supply.) Experiments with animals and humans have demonstrated that only small fractions of absorbed 1,1,1-trichloroethane doses (<10%) are metabolized, regardless of the route of exposure. The toxicokinetic behavior of 1,1,1-trichloroethane has the same qualitative pattern in humans, rats, and mice; however, some quantitative differences among these species have been observed, including a higher blood:air partition coefficient and an increased rate of metabolism in mice compared with rats and humans. Physiologically-based pharmacokinetic models have been developed to describe the kinetic behavior of

significantly influence systemic absorption of 1,1,1-trichloroethane. 1,1,1-Trichloroethane is poorly metabolized (Dallas et al. 1989) (see Section 3.4.3). in all species?

Animal experiments provide supporting evidence that inhaled 1,1,1-trichloroethane is rapidly and extensively absorbed and that the absorption, during short-term exposures, is influenced by ventilation rate. In rats exposed to 50 or 500 ppm, percentage uptake decreased from ≈80% at the onset of exposure to ≈50% after 2 hours of exposure to 50 or 500 ppm. 1,1,1-Trichloroethane was detected in arterial blood within 2 minutes of the onset of exposure and approached steady-state concentrations within 2 hours (Dallas et al. 1989). In anesthetized dogs under regulated respiration conditions, 1,1,1-trichloroethane was detected in arterial blood within 2 minutes of the onset of exposure to 700, 1,500, or 3,000 ppm. Arterial blood concentrations approached steady-state levels within 1 hour at 700 ppm, but not at 1,500 or 3,000 ppm; absorption increased with increases in pulmonary ventilation rate (Hobara et al. 1982, 1983a, 1983b).

3.4.1.2 Oral Exposure

Data regarding the rate or extent of absorption of ingested 1,1,1-trichloroethane in humans are not available, but based on extensive animal data, it is anticipated that oral absorption of 1,1,1-trichloroethane will be extensive in humans. Animal experiments indicate that 1,1,1-trichloroethane is rapidly and completely absorbed by the gastrointestinal tract. Maximum levels of 1,1,1-trichloroethane in venous blood of rats were detected within 10–15 minutes of gavage administration of a 14.2 mg/kg dose in water (Reitz et al. 1988). In experiments in which rats were given an 8-hour free access to drinking water containing [2-^{14}C]-labeled 1,1,1-trichloroethane, radioactivity in expired air, urine, and selected tissues (assayed 56 hours following cessation of access to the labeled water) represented 95.2% of the average dose of 116 mg/kg, indicating nearly complete absorption of the administered dose (Reitz et al. 1988). In experiments with rats and mice given single gavage doses of radiolabeled 1,1,1-trichloroethane in vegetable oil ranging from 100 to 3,000 mg/kg, dose-recovery in expired air ranged from 90 to 97% (RTI 1987). Nearly complete absorption of orally administered 1,1,1-trichloroethane was also indicated in experiments in which rats or mice were pretreated with daily doses of the compound in corn oil for 4 weeks (3,000 and 1,000 mg/kg/day for rats and mice, respectively) before radiolabeled compound was administered to measure absorption and elimination. Radioactivity in expired air and urine (collected for 48 hours after administration) accounted for 88–98% of the administered doses (Mitoma et al. 1985).

3.4.2.2 Oral Exposure

No studies were located regarding the distribution of 1,1,1-trichloroethane to human tissue after oral exposure to the compound. Ingested 1,1,1-trichloroethane, however, is probably widely distributed among tissues, with preferential accumulation in fatty tissues, based on results of animal studies. Distribution of 1,1,1-trichloroethane to tissues will be governed by several factors, including tissue blood flow rate, tissue volume, and tissue:blood partition coefficient, the latter factor being probably the most important. Following gavage administration of 1,1,1-trichloroethane in vegetable oil to rats (100, 300, or 1,000 mg/kg) or mice (300, 1,000, or 3,000 mg/kg), the compound was distributed to tissues throughout the body, with preferential accumulation in fatty tissues (RTI 1987).

3.4.2.3 Dermal Exposure

No studies were located regarding the distribution of 1,1,1-trichloroethane among human or animal tissues following dermal exposure; however, dermally applied 1,1,1-trichloroethane, once absorbed, is probably widely distributed among tissues, with preferential accumulation in fatty tissues, based on results from oral and inhalation studies with animals.

3.4.2.4 Other Routes of Exposure

Measurements of the tissue distribution of ^{14}C-1,1,1-trichloroethane or its metabolites in rats or mice 24 hours after an intravenous injection indicate a distribution pattern similar to that after oral or inhalation exposure; adipose tissue contained higher concentrations than skeletal muscle, liver, or skin tissue (RTI 1987).

3.4.3 Metabolism

Metabolism appears to play a relatively minor role in the overall disposition of 1,1,1-trichloroethane in humans and animals. Only a small fraction of the absorbed dose (<10%) is metabolized; a large fraction of the absorbed dose is excreted unchanged in exhaled air, regardless of the exposure route. In humans exposed to 70 or 145 ppm 1,1,1-trichloroethane in air for 4 hours, an estimated 60–80% of the absorbed compound was excreted unchanged in exhaled breath (Monster et al. 1979). Metabolites in urine,

trichloroethanol and trichloroacetic acid, collected for 70 hours postexposure represented approximately 2 and 0.5% of the 1,1,1-trichloroethane initially absorbed. In humans exposed to 35 or 350 ppm for 6 hours, >91% of absorbed 1,1,1-trichloroethane was excreted unchanged by the lungs, 5–6% was metabolized and excreted as trichloroethanol and trichloroacetic acid, and <1% remained in the body after 9 days (Nolan et al. 1984).

In rats and mice dosed by gavage with 1,1,1-trichloroethane in vegetable oil 5 days/week for 4 weeks, followed by a single dose of ^{14}C-labeled compound, 85.1 and 92.3% of the respective doses were recovered as unchanged compound in expired air; respective recovery percentages of metabolite fractions (48 hours after administration) in rats and mice were 0.9 and 2.0% as CO_2, 2.1 and 3.4% as metabolites in urine, and 1.2 and 0.7% as presumed metabolites remaining in the carcasses (Mitoma et al. 1985). Similarly, exhalation of unchanged compound was the predominant pathway for elimination of absorbed 1,1,1-trichloroethane, accounting for >90% of doses administered in drinking water studies with rats (Reitz et al. 1988) and in inhalation studies with rats and mice (Schumann et al. 1982a). Comparison of metabolic disposition in mice and rats indicated that mice metabolized 2–3 times more 1,1,1-trichloroethane on a body weight basis; however, in both species, metabolism was a dose-dependent, saturable process that represented a minor route of elimination (Schumann et al. 1982a, 1982b).

Analysis of urine following human and animal exposure to 1,1,1-trichloroethane identified trichloroethanol, trichloroethanol glucuronide, and trichloroacetic acid as major metabolites of 1,1,1-trichloroethane; CO_2, identified in exhaled breath, is the other major metabolite (Kawai et al. 1991; Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; Schumann et al. 1982a). Figure 3-3 illustrates a general metabolic scheme for 1,1,1-trichloroethane. The initial oxidation step is thought to be catalyzed by the microsomal cytochrome P-450 mixed-function oxidase system. In vitro reaction mixtures containing rat hepatic microsomes and nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) oxidize 1,1,1-trichloroethane to trichloroethanol. 1,1,1-Trichloroethane metabolism significantly increased when microsomes from rats pretreated with phenobarbital, an inducer of certain isozymes of cytochrome P-450, were used. This finding provides supporting evidence of the involvement of this enzyme system in the metabolism, albeit limited, of 1,1,1-trichloroethane (Ivanetich and Van den Honert 1981; Koizumi et al. 1983). The pathway for conversion of trichloroethanol to trichloroacetic acid presumably involves the intermediate formation of chloral hydrate and may involve alcohol and aldehyde dehydrogenases or cytochrome P-450 mixed-function oxidases (Casciola and Ivanetich 1984; Ivanetich and Van den Honert 1981). Although trichloroacetic acid or chloral hydrate were not detected as in vitro

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

After acute exposure, most inhaled 1,1,1-trichloroethane is rapidly excreted unchanged in expired air of humans and animals. Within 1 hour of administration, humans exhaled 44% of the radioactivity they had inhaled from a single breath of radiolabeled 1,1,1-trichloroethane (Morgan et al. 1970). Humans exposed to 70 or 145 ppm for 4 hours exhaled 60–80% of inhaled 1,1,1-trichloroethane unchanged during a 150-hour period after exposure (Monster et al. 1979). Other humans exposed to 35 or 350 ppm for 6 hours exhaled >91% of absorbed 1,1,1-trichloroethane as the unchanged compound within 9 days of exposure (Nolan et al. 1984). Similar observations were made in studies of rats (Ikeda and Ohtsuji 1972; Schumann et al. 1982a, 1982b), mice (Schumann et al. 1982a, 1982b), and anesthetized dogs (Hobara et al. 1982). Nolan et al. (1984) described the temporal elimination pattern for 1,1,1-trichloroethane in blood and expired air of humans as "triexponential" and estimated half-lives of 44 minutes, 5.7 hours, and 53 hours for the initial, intermediate, and terminal phases, respectively. Raymer et al. (1991) used a two-compartment model to fit experimental observations of the temporal decrease in 1,1,1-trichloroethane concentrations in human breath samples collected for 4 hours after exposure to contaminated atmospheres; elimination half-lives ranged from 0.00 to 0.17 hours for the first compartment and from 1.80 to 6.08 hours for the second compartment.

Exhalation of CO_2 and urinary excretion of metabolites (trichloroethanol and trichloroacetic acid) represent minor elimination pathways for inhaled 1,1,1-trichloroethane. Nevertheless, observed correlations between urinary concentrations of 1,1,1-trichloroethane metabolites and exposure concentrations indicate that urine analysis may be a useful method of exposure assessment (Caperos et al. 1982; Ghittori et al. 1987; Imbriani et al. 1988; Kawai et al. 1991; Mizunuma et al. 1995; Seki et al. 1975). Estimated half-lives for the elimination of trichloroethanol and trichloroacetic acid from human blood after inhalation exposures to 1,1,1-trichloroethane were 10–27 hours for trichloroethanol and 70–85 hours for trichloroacetic acid (Monster et al. 1979; Nolan et al. 1984). The long half-life of trichloroacetic acid is due to binding of this metabolite to plasma proteins. Daily occupational exposure to 1,1,1-trichloroethane progressively increased urinary metabolite levels during the workweek, while levels decreased over the weekend (Seki et al. 1975). This observation is consistent with observations of the rapid clearance of 1,1,1-trichloroethane and its metabolites from animal tissues after inhalation exposure (Dallas et al. 1989; Holmberg et al. 1977; Schumann et al. 1982a, 1982b; Takahara 1986a).

3.4.4.2 Oral Exposure

Humans eliminate ingested 1,1,1-trichloroethane in their exhaled breath (Stewart and Andrews 1966), but no studies were located that quantified excretion rates or the extent of excretion. The pattern of elimination is expected to be similar to that of inhaled 1,1,1-trichloroethane (i.e., exhalation of unchanged 1,1,1-trichloroethane should be the predominant route of excretion; exhalation of CO_2 and urinary excretion of other metabolites are minor routes). This pattern has been observed in animals after inhalation (see Section 3.4.4.1) and oral exposure (Mitoma et al. 1985; Reitz et al. 1988; RTI 1987). In rats exposed to 1,1,1-trichloroethane in drinking water for 8 hours (total dose of 116 mg/kg), the primary route of excretion was rapid elimination of unchanged 1,1,1-trichloroethane in expired air; only 3% of the ingested dose was metabolized (Reitz et al. 1988). Essentially all of the ingested 1,1,1-trichloroethane was excreted within 30 hours. Similar results were obtained in gavage studies with rats and mice (Mitoma et al. 1985; RTI 1987). Excretion via the mother's milk does not appear to be a significant route of excretion for 1,1,1-trichloroethane. Approximately 0.04% of an orally-administered dose of 1,1,1-trichloroethane was excreted in the 24-hour milk of lactating goats (Hamada and Tanaka 1995).

3.4.4.3 Dermal Exposure

The pattern of excretion in humans after dermal exposure is expected to be similar to that of inhaled 1,1,1-trichloroethane: rapid exhalation of 1,1,1-trichloroethane in expired air is the major excretion route; exhalation of CO_2 and urinary excretion of other metabolites are minor routes (see Section 3.4.4.1). Several studies have measured 1,1,1-trichloroethane in the expired breath of humans after (and during) short-term dermal exposure to 1,1,1-trichloroethane (Fukabori et al. 1977; Riihimaki and Pfaffli 1978; Stewart and Dodd 1964), but 1,1,1-trichloroethane exhalation as a percentage of absorbed dose was not quantitated in these studies.

3.4.4.4 Other Routes of Exposure

Results in animals given 1,1,1-trichloroethane injections indicate that excretion patterns in animals are similar regardless of route. In mice given intraperitoneal injections of 1,1,1-trichloroethane, 88% of the dose was excreted unchanged in expired air and 1% was excreted as metabolites in urine (Takahara 1986b). In rats given intraperitoneal injections, 98.7% of the dose was exhaled as unchanged 1,1,1-trichloroethane (Hake et al. 1960). Within 24 hours of intravenous injection of radiolabeled 1,1,1-trichloro-

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

1,1,1-Trichloroethane is rapidly and extensively absorbed from the lungs (Astrand et al. 1973; Dallas et al. 1989; Hobara et al. 1982, 1983a, 1983b; Monster et al. 1979; Morgan et al. 1972a, 1972b; Nolan et al. 1984), skin (Fukabori et al. 1977; Morgan et al. 1991; Riihimaki and Pfaffli 1978; Stewart and Dodd 1964; Tsuruta 1975) and gastrointestinal tract (Mitoma et al. 1985; Reitz et al. 1988; RTI 1987; Stewart and Andrews 1966). The lipophilic nature of 1,1,1-trichloroethane, the rates of absorption upon various routes of exposure, and the rates at which the chemical leaves the body in expired air when exposure is terminated all suggest that 1,1,1-trichloroethane is very likely transported across cellular membranes by passive diffusion. No known specific intermediary molecules influence the distribution of 1,1,1-trichloroethane among tissues in the body. The lipophilicity and volatility of 1,1,1-trichloroethane, along with the low rates at which it is metabolized, appear to be the most important factors influencing distribution within and elimination from the body. The compound is widely distributed by the blood among tissues, with preferential accumulation in fatty tissues, and is rapidly cleared following exposure cessation (Holmberg et al. 1977; RTI 1987; Schumann et al. 1982a, 1982b; Takahara 1986b).

As presented in detail in Section 3.4.3, only a small percentage of 1,1,1-trichloroethane absorbed across the lung is metabolized; most of the absorbed dose is excreted unchanged from the lung. For example, a 6-hour exposure to 35 or 350 ppm of 1,1,1-trichloroethane resulted in the metabolism of approximately 5–6% of the absorbed dose, which was excreted in the urine as trichloroethanol or trichloroacetic acid (Nolan et al. 1984). More than 90% was excreted unchanged from the lungs and <1% remained in the body after 9 days. Analysis of urine following human and animal exposure to 1,1,1-trichloroethane identified trichloroethanol, trichloroethanol glucuronide, and trichloroacetic acid as major metabolites of 1,1,1-trichloroethane; CO_2, identified in exhaled breath, is the other major metabolite (Kawai et al. 1991; Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; Schumann et al. 1982a). Figure 3-3 illustrates a general metabolic scheme for 1,1,1-trichloroethane. The initial oxidation step is thought to be catalyzed by the microsomal cytochrome P-450 mixed-function oxidase system. The pathway for conversion of trichloroethanol to trichloroacetic acid presumably involves the intermediate formation of chloral hydrate and may involve alcohol and aldehyde dehydrogenases or cytochrome P-450 mixed-function oxidases (Casciola and Ivanetich 1984; Ivanetich and Van den Honert 1981). The pattern of elimination following oral or dermal exposure is expected to be similar to that of inhaled 1,1,1-tri-

chloroethane (i.e., exhalation of unchanged 1,1,1-trichloroethane should be the predominant route of excretion; exhalation of CO_2 and urinary excretion of other metabolites are minor routes).

3.5.2 Mechanisms of Toxicity

The mechanism by which high levels of 1,1,1-trichloroethane produces mild to moderate hepatotoxic effects in humans and animals is only partially understood. Studies of more potent hepatotoxic chlorinated alkanes (including carbon tetrachloride, chloroform, and 1,1,2-trichloroethane) have clearly demonstrated an involvement of cytochrome P-450-mediated dechlorination in the production of liver injury (Plaa 1986). It has been hypothesized that the production of free radicals via the homolytic cleavage of the carbon-chlorine bond in these hepatotoxic chlorinated alkanes occurs in the endoplasmic reticulum of hepatocytes, and that the free radicals react with unsaturated lipids and proteins in the endoplasmic reticulum, producing lipid peroxidation and covalent binding. These actions lead to morphological and functional changes in this organelle and, eventually, to cellular dysfunction (triglyceride accumulation) and necrosis (Plaa 1986). The potency of the 1,1,2- isomer of trichloroethane to produce liver injury is markedly greater than that of the 1,1,1- isomer (Carlson 1973; Takahara 1986c). This difference has been associated with differences in the metabolic activation of the two isomers. 1,1,2-Trichloroethane is metabolized to a much greater extent in mice and rats after gavage administration than is 1,1,1-trichloroethane. Urinary excretion of metabolites accounted for >70% of the administered doses of the 1,1,2- isomer; in contrast, >85% of the administered 1,1,1- isomer dose was excreted unchanged in expired air (Mitoma et al. 1985). In experiments with rat liver microsomes, Van Dyke and Wineman (1971) observed that 9.8% of the chloride was enzymatically removed from the 1,1,2- isomer, compared with <0.5% removal of chloride from the 1,1,1- isomer in the same period. The difference in extent of metabolism of the 1,1,2- and 1,1,1- isomers explains the difference in hepatotoxicity of the two compounds (i.e., the 1,1,2- isomer is more potent because greater quantities of reactive metabolites are produced from it); however, whether the mild hepatotoxicity of 1,1,1-trichloroethane is mediated by a metabolite or by the compound itself is unclear. Carlson (1973) reported that rats pretreated with phenobarbital displayed signs of liver injury (increased levels of SGPT and SGOT and decreased activity of glucose-6-phosphatase) immediately following a 2-hour exposure to 11,600 ppm 1,1,1-trichloroethane; these signs were not apparent in nonpretreated rats exposed to the same 1,1,1-trichloroethane concentration or in rats that had received only the phenobarbital pretreatment. This suggests that metabolic activation is involved in the expression of 1,1,1-trichloroethane's hepatotoxicity. Another

study, however, did not find that phenobarbital pretreatment potentiated the hepatotoxicity of 1,1,1-trichloroethane (Cornish et al. 1973).

Acute exposures to high 1,1,1-trichloroethane concentrations can cause sudden death in humans due to ventricular fibrillation, myocardial depression, or respiratory arrest. Animal studies show that arrhythmias (that can lead to ventricular fibrillation) can be produced by exogenously administered epinephrine during or immediately after inhalation exposure to 1,1,1-trichloroethane (Carlson 1981; Clark and Tinston 1973; Reinhardt et al. 1973; Trochimowicz et al. 1974). 1,1,1-Trichloroethane is one of the most potent of the volatile organic compounds that induce arrhythmias. The studies indicate that the arrhythmias are not caused directly by 1,1,1-trichloroethane, but result from its sensitization of the heart to epinephrine. The basis for the sensitization is not completely understood, but evidence suggests that the sensitization is produced by 1,1,1-trichloroethane itself and not by its metabolites. Carlson (1981) reported that pretreatment of rabbits with phenobarbital (thereby increasing 1,1,1-trichloroethane metabolism) did not increase the incidence of epinephrine-induced arrhythmias during 1-hour exposures to 5,600 ppm, and that treatment with cytochrome P-450 inhibitors (SKF-525A and Lilly 18947) (decreasing the metabolism of 1,1,1-trichloroethane) 30 minutes before exposure to 1,1,1-trichloroethane increased the incidence of epinephrine-induced cardiac arrhythmias. The arrhythmogenicity of 1,1,1-trichloroethane and other halogenated hydrocarbons may involve intercellular communication inhibition, presumably through parent-compound modification of gap junctions between cardiac myocytes. Toraason et al. (1992) demonstrated that a series of halogenated hydrocarbons, including 1,1,1-trichloroethane, inhibited the transfer of a fluorescent probe between adjacent cultured cardiac myocytes isolated from neonatal rats (an assay for gap junction communication) and that the inhibition was not affected by pretreating the cells with SKF-525A. Toraason et al. (1992) noted that the ability of the compounds to inhibit intercellular communication paralleled their ability to sensitize the heart to epinephrine-induced arrhythmias.

Acute exposure to high concentrations of 1,1,1-trichloroethane (≈10,000–26,000 ppm) lowered blood pressure in humans and animals within minutes of exposure (Herd et al. 1974; Kobayashi et al. 1988; McLeod et al. 1987; Wright and Strobl 1984). Studies with anesthetized dogs associated the decrease in blood pressure with peripheral vasodilation at the lower end of the effective concentration range and with decreased heart rate and myocardial contractility at higher concentrations (Herd et al. 1974; Kobayashi et al. 1988). Intravenous administration of phenylephrine (an agent that putatively constricts peripheral vasculature) or calcium counteracted the blood pressure-reducing effects of 1,1,1-trichloroethane in

Monster (1986) proposed that the best method for estimating occupational exposure to 1,1,1-trichloroethane was to determine the levels of 1,1,1-trichloroethane and trichloroacetic acid in blood after work on Fridays. Results of Mizunuma et al. (1995) indicated that urinary levels of 1,1,1-trichloroethane (as parent compound) were more closely correlated to 1,1,1-trichloroethane in the ambient air of a group of 50 solvent workers than the major urinary metabolites, trichloroethanol and trichloroacetic acid. These results indicate that urinary levels of parent compound may be the best indicator of occupational exposure to 1,1,1-trichloroethane.

The length of time between 1,1,1-trichloroethane exposure and the measurement of breath, blood, or urine levels is critical to the accurate evaluation of the magnitude of exposure. Up to 90% of the 1,1,1-trichloroethane absorbed by any route is rapidly excreted unchanged in the expired air (Monster et al. 1979; Morgan et al. 1970, 1972b; Nolan et al. 1984; Stewart et al. 1961, 1969). Most of the remaining 10% is accounted for as the urinary metabolites trichloroethanol and trichloroacetic acid. Furthermore, 1,1,1-trichloroethane is rapidly eliminated from the body; ≥99% is eliminated within 50 hours (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984; Stewart et al. 1961). See Section 3.4 for more information regarding the pharmacokinetics of 1,1,1-trichloroethane. The appearance of trichloroacetic acid in urine is not unique to 1,1,1-trichloroethane, as it has also been identified as a urinary metabolite of trichloroethylene and tetrachloroethylene (Monster 1988). If exposure is known to be solely to 1,1,1-trichloroethane, trichloroacetic acid levels in the urine may be a useful biomarker of exposure, because of the relatively long half-life of trichloroacetic acid.

3.8.2 Biomarkers Used to Characterize Effects Caused by 1,1,1-Trichloroethane

The central nervous system is apparently the most sensitive tissue to 1,1,1-trichloroethane exposure. Decreased psychomotor performance, altered EEG recordings, ataxia, and anesthesia have been observed in humans after acute exposure (Dornette and Jones 1960; Mackay et al. 1987; Muttray et al. 2000; Stewart et al. 1975; Torkelson et al. 1958). Mild hepatic effects and decreased blood pressure have also been noted (Cohen and Frank 1994; Croquet et al. 2003; Dornette and Jones 1960; Stewart et al. 1961; Texter et al. 1979). Numerous animal studies provide supporting evidence for the sensitivity of the central nervous system to acute and intermediate-duration exposure to 1,1,1-trichloroethane. Adverse cardiovascular effects and mild hepatic effects have also been observed in animals. Indices of central nervous system, hepatic, and cardiovascular effects are of limited value as biomarkers, since many other

lipophilic chemicals (including some likely to be present at the same sites as 1,1,1-trichloroethane) may cause similar effects in these target organs.

No specific biomarkers of effects caused by 1,1,1-trichloroethane were found in the literature. Additional information regarding the effects of exposure to 1,1,1-trichloroethane can be found in OTA (1990) and CDC/ATSDR (1990). For a more detailed discussion of the health effects caused by 1,1,1-trichloroethane see Section 3.2.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Although there are no reports of chemical interactions in humans, several animal studies have identified possible interactions between 1,1,1-trichloroethane and other chemicals.

Ethanol, when given orally to mice at doses of 0.125–2.0 g/kg, potentiated both the lethality and behavioral effects (inverted screen test) of inhaled 1,1,1-trichloroethane at concentrations ranging from ≈200 to 10,000 ppm (Woolverton and Balster 1981). In another study, a 3-day pretreatment of mice with ethanol enhanced 1,1,1-trichloroethane-induced liver toxicity, as indicated by an assay of liver function (bromosulfophthalein retention in plasma), but not an assay of liver damage (SGPT levels) (Klaassen and Plaa 1966). Other studies, using only serum enzyme levels to assay liver damage (SGPT or SGOT), found that ethanol markedly and consistently enhanced the hepatotoxicity of more potent chlorinated compounds such as carbon tetrachloride or trichloroethylene, but had no effect on the hepatotoxicity of 1,1,1-trichloroethane (Cornish and Adefuin 1966; Klaassen and Plaa 1967). Ethanol may potentiate the hepatotoxicity of chlorinated alkanes because of its ability to induce cytochrome P450IIE1 (Ikatsu and Nakajima 1992). The available data indicate that ethanol can enhance the acute neurobehavioral effects of 1,1,1-trichloroethane, but will not cause 1,1,1-trichloroethane to produce severe liver damage (necrosis) like that caused by other chlorinated alkanes such as carbon tetrachloride or 1,1,2-trichloroethane.

Co-exposure of control or ethanol-treated rats to inhaled concentrations of 10 ppm carbon tetrachloride and 200 ppm 1,1,1-trichloroethane did not produce changes in several indices of liver damage (SGPT, SGOT, and liver malondialdehyde) compared with exposure to 10 ppm carbon tetrachloride alone (Ikatsu and Nakajima 1992). This indicates that 1,1,1-trichloroethane may be protective against hepatotoxic

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,1,1-trichloroethane than will most persons exposed to the same level of 1,1,1-trichloroethane in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of 1,1,1-trichloroethane, or compromised function of organs affected by 1,1,1-trichloroethane. Populations who are at greater risk due to their unusually high exposure to 1,1,1-trichloroethane are discussed in Section 6.7, Populations With Potentially High Exposures.

Limited data from animal studies (Woolverton and Balster 1981) indicate that alcohol drinkers may be more susceptible to the acute neurobehavioral effects of 1,1,1-trichloroethane. Moderate to heavy alcohol drinkers may be more susceptible to the hepatotoxicity of some chlorinated alkanes, such as carbon tetrachloride, chloroform, and 1,1,2-trichloroethane, due to ethanol induction of hepatic cytochrome P-450 isozymes involved in the activation of these compounds to intermediate hepatotoxic metabolites. Available animal studies (Cornish and Adefuin 1966; Klaassen and Plaa 1966, 1967), however, have not demonstrated that ethanol ingestion will potentiate the hepatotoxicity of 1,1,1-trichloroethane. Furthermore, evidence indicates that ethanol does not cause 1,1,1-trichloroethane and carbon tetrachloride to interact synergistically to produce hepatotoxic effects, although such an interaction has been demonstrated for ethanol, carbon tetrachloride, and chloroform (Ikatsu and Nakajima 1992). The available data suggest that alcohol ingestion is not likely to significantly potentiate the hepatotoxicity of 1,1,1-trichloroethane.

Diabetics consistently in a state of ketosis may be more susceptible to the hepatotoxicity of certain chlorinated alkanes including carbon tetrachloride, chloroform, and 1,1,2-trichloroethane, due to a potentiation from increased ketone levels in the body. Animal studies indicate that the ketone potentiation of the hepatotoxicity of chlorinated alkanes involves an enhancement of the metabolic production of hepatotoxic intermediate metabolites. Available data, however, indicate that ketones do not appreciably potentiate the hepatotoxicity of 1,1,1-trichloroethane (Plaa 1986, 1988). Thus, diabetics in a state of ketosis are not likely to be more susceptible to the hepatotoxicity of 1,1,1-trichloroethane than the population at large.

Because 1,1,1-trichloroethane is associated with some cardiovascular effects (see Section 3.2.1.2), persons with compromised heart conditions may be at additional risk around high exposure levels of 1,1,1-trichloroethane and should be restricted to some lower level of exposure.

Although no data are available that address this issue, it is possible that individuals with impaired respiratory function (e.g., emphysema, poor perfusion) might excrete less 1,1,1-trichloroethane in a given period than other people, since most of a single dose is expired (Monster et al. 1979; Nolan et al. 1984). In situations of prolonged exposure, such as living near a hazardous waste site, this might contribute to accumulation of 1,1,1-trichloroethane in the body. People with respiratory disease might, therefore, constitute a more susceptible population.

Young people might be unusually susceptible to 1,1,1-trichloroethane, since the nervous system continues to develop in humans after birth and this chemical may produce residual neurological effects. Developmental toxicity data in humans are not available to address this question. Neurobehavioral testing of exposed rat pups was negative in one study (York et al. 1982). Delays in developmental milestones (pinnae detachment, incisor eruption, and eye opening) and impaired performance in neurobehavior tests were noted in mouse pups of dams exposed to 1,1,1-trichloroethane during later stages of gestation at levels that did not result in apparent maternal toxicity (Jones et al. 1996). These results suggest that developing organisms may be more susceptible than adults to the toxic effects of 1,1,1-trichloroethane. However, Jones et al. (1996) reported delays in developmental milestones (pinnae detachment, incisor eruption, and eye opening) and impaired neurobehavioral performance in mouse pups of dams exposed to 1,1,1-trichloroethane during later stages of gestation. These results indicate that children might be more susceptible to 1,1,1-trichloroethane than adults.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,1,1-trichloroethane. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 1,1,1-trichloroethane. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide

specific information about treatment following exposures to halogenated hydrocarbon solvents, such as 1,1,1-trichloroethane:

Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. 2nd edition. Baltimore, MD: Williams & Wilkins, 1436-1440.

Parraga M, West JM. 1998. Hydrocarbons. In: Viccellio P, ed. Emergency toxicology. 2nd edition. Philadelphia, PA: Lippincott-Raven Publishers, 299-313.

3.11.1 Reducing Peak Absorption Following Exposure

Ingested 1,1,1-trichloroethane is rapidly absorbed by the gastrointestinal tract of humans and animals (Mitoma et al. 1985; Reitz et al. 1988; RTI 1987; Stewart and Andrews 1966). To minimize absorption following ingestion, several treatments have been suggested, including administration of milk or water to dilute the gastrointestinal tract contents, gastric lavage, and administration of emesis-inducing compounds or activated charcoal (Goldfrank et al. 1990; Stutz and Janusz 1988). Butter or some other food high in lipids might be given. The lipids will serve to delay substantially, and possibly diminish, systemic absorption of the 1,1,1-trichloroethane. It should be noted, however, that upon induction of emesis, there is the possibility of aspiration of 1,1,1-trichloroethane into the lungs, which may result in pneumonia. Therefore, treatment via stomach pump has been recommended. Due to rapid absorption of 1,1,1-trichloroethane by the gut, any measures to retard absorption must be taken very rapidly.

Inhaled 1,1,1-trichloroethane is rapidly absorbed and expired, predominantly unchanged, through the lungs (see Section 3.4.). The rapidity with which inhaled 1,1,1-trichloroethane is absorbed (Astrand et al. 1973; Morgan et al. 1972a, 1972b) indicates that assisted ventilation or positive pressure ventilation techniques will not prevent the absorption of 1,1,1-trichloroethane in the lung and emphasizes the importance of removing the subject from the contaminated atmosphere. Nevertheless, such techniques have been suggested to help eliminate the compound from the body (Bronstein and Currance 1988).

The volatility of 1,1,1-trichloroethane is likely to limit absorption of the dermally applied compound, even though dermal absorption under conditions that prevent evaporation is rapid and extensive (Fukabori et al. 1977; Morgan et al. 1991; Stewart and Dodd 1964; Tsuruta 1975). Washing the skin with soapy water has been suggested to reduce the absorption of dermally applied 1,1,1-trichloroethane (Bronstein and Currance 1988; Goldfrank et al. 1990; Stutz and Janusz 1988). Ethyl or isopropyl alcohol also could

be used to dilute 1,1,1-trichloroethane on the skin. Flushing the exposed eye with large quantities of water or saline for 15–30 minutes has been suggested to prevent absorption and soothe irritation (Bronstein and Currance 1988; Stutz and Janusz 1988).

3.11.2 Reducing Body Burden

When exposure to 1,1,1-trichloroethane ceases, regardless of route of exposure, the compound is rapidly cleared from the body, predominantly by exhalation of unchanged 1,1,1-trichloroethane in expired air (see Section 3.4.). Very little metabolism of the compound takes place, and despite a preferential distribution of absorbed 1,1,1-trichloroethane to fatty tissues, significant retention does not occur without continued exposure. Thus, continued ventilation by the lungs will eliminate the compound from the body. Suggested methods to assist in lung ventilation include orotracheal and nasotracheal intubation for airway control and positive pressure ventilation techniques (Bronstein and Currance 1988; Ellenhorn and Barceloux 1988).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Suggested methods to treat the effects of acute exposure to 1,1,1-trichloroethane are primarily supportive, rather than active, and are not generally directed against a particular mechanism of action (Bronstein and Currance 1988; Ellenhorn and Barceloux 1988; Ellenhorn et al. 1997; Goldfrank et al. 1990; Herd et al. 1974; Stutz and Janusz 1988; Parraga and West 1998). Suggested methods of treatment include removing the subject from the source of exposure, ventilation assistance, gastric dilution and lavage for ingested material, oxygen administration, and skin washing. Continuous cardiac monitoring is routine for exposed patients. These methods rely on the body's ability to eliminate rapidly 1,1,1-trichloroethane and its metabolites. Mechanisms of action, however, are discussed in this section in relation to the possible development of interfering treatment methods.

The mechanism by which 1,1,1-trichloroethane and other organic solvents depress the central nervous system is poorly understood, but is thought to involve interactions of the parent compound with lipids and/or proteinaceous components of neural membranes (Evans and Balster 1991). No known methods specifically counteract the central nervous system effects of 1,1,1-trichloroethane. Because the specific cellular or biochemical nature of central nervous system depression is poorly understood, it is difficult to

propose any method to interfere with this effect of 1,1,1-trichloroethane, other than to prevent further exposure to the compound so that it can be cleared from the body.

The acute cardiotoxic effects of 1,1,1-trichloroethane (reduced blood pressure and increased sensitization to epinephrine-induced arrhythmias) appear to be mediated by the compound and not its metabolites (Carlson 1973; Toraason et al. 1990, 1992) and have been associated with the ability of 1,1,1-trichloroethane to interfere with membrane-mediated processes including calcium mobilization during myocardial contraction (Herd et al. 1974; Hoffman et al. 1992; Toraason et al. 1990) and gap junction communication between myocardial cells (Toraason et al. 1992). The administration of epinephrine to counteract 1,1,1-trichloroethane-induced cardiovascular depression has been cautioned against, because of the risk of arrhythmias and ventricular fibrillation (Bronstein and Currance 1988; Goldfrank et al. 1990; Herd et al. 1974). Herd et al. (1974) demonstrated that intravenous injection or infusion of calcium (as calcium gluconate) or phenylephrine protected against 1,1,1-trichloroethane-induced blood pressure reduction in anesthetized dogs and suggested more detailed study to assess whether these compounds could be used routinely to resuscitate exposed individuals. Exogenous calcium appears to counteract the influence of 1,1,1-trichloroethane on calcium mobilization during myocardial contraction (Herd et al. 1974; Hoffman et al. 1992; Toraason et al. 1990). Evidence indicates that phenylephrine counteracts 1,1,1-trichloroethane-induced vasodilation without influencing myocardial function (Herd et al. 1974). Further studies examining these active methods of treatment were not located.

Unlike more potent chlorinated alkanes such as carbon tetrachloride or 1,1,2-trichloroethane, it is not clear whether the hepatotoxicity of 1,1,1-trichloroethane is due to a metabolite or the parent compound (see Section 3.5). If metabolites produced by cytochrome P-450 oxidation or dechlorination are responsible for the hepatotoxicity, administering cytochrome P-450 inhibitors (e.g., SKF-525A) may inhibit the development of toxic effects on the liver. Clinical or animal studies examining the use of such an approach and the possibility of side effects, however, were not located.

3.12 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1,1-trichloroethane is available. Where

adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,1,1-trichloroethane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed. In view of the apparent decision to stop producing this cmpd. in 2002-2005, is it really necessary to develop a research agenda at this point?

3.12.1 Existing Information on Health Effects of 1,1,1-Trichloroethane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1,1-trichloroethane are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,1,1-trichloroethane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Several case studies have documented the lethality of high concentrations of inhaled 1,1,1-trichloroethane. Experimental studies, as well as case reports, have reported on acute systemic and neurological effects. Chronic systemic, neurological, developmental, and reproductive effects have been investigated in epidemiology studies. Health effects caused by other routes of administration have not been as well studied in humans. One case study regarding oral exposure to 1,1,1-trichloroethane reported acute systemic effects and investigated potential neurological effects. Developmental effects and cancer from exposure to drinking water were investigated by epidemiology studies. The effects of dermal exposure

difficult to do since most studies are case studies

are discussed in case reports regarding peripheral neuropathy and dermal sensitization in workers and in controlled studies regarding skin irritation.

As indicated in Figure 3-6, many aspects of the health effects resulting from inhalation, ingestion, and dermal exposure to 1,1,1-trichloroethane have been studied in animals. Except for genotoxicity, each of the end points has been investigated in animals exposed to 1,1,1-trichloroethane by the inhalation and oral routes. Fewer end points have been studied following dermal exposure.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. The primary target organs of 1,1,1-trichloroethane toxicity have been identified from human and animal studies. The central nervous system appears to be the most sensitive target organ after inhalation exposure. Decreased psychomotor performance, altered EEG, ataxia, and anesthesia have been observed in humans after inhalation exposure (Dornette and Jones 1960; Gamberale and Hultengren 1973; Mackay et al. 1987; Muttray et al. 2000; Stewart et al. 1961, 1969, 1975; Torkelson et al. 1958). Cardiovascular effects (decreased blood pressure and arrhythmias) and mild hepatic effects (increased serum enzyme levels, fatty liver, cholestasis) have also been observed (Cohen and Frank 1994; Croquet et al. 2003; Dornette and Jones 1960; Guberan et al. 1976; Halevy et al. 1980; Hodgson et al. 1989; Krantz et al. 1959; MacDougall et al. 1987; Stewart 1971; Stewart et al. 1961; Texter et al. 1979; Travers 1974). Developmental toxicity studies in rats and rabbits indicated that 1,1,1-trichloroethane can cause mild developmental delays and effects in the offspring at high levels (usually accompanied by significant maternal toxicity) (BRRC 1987a, 1987b; Jones et al. 1996; York et al. 1982). Acute oral studies have determined lethal levels in animals and have shown that ingested 1,1,1-trichloroethane produces neurological effects and reduced body weight gain in animals, and perhaps mild liver effects as well (Bruckner et al. 2001; Spencer et al. 1990; Torkelson et al. 1958; Tyson et al. 1983). The only human data on ingested 1,1,1-trichloroethane was a single case report (Stewart and Andrews 1966). The distribution of 1,1,1-trichloroethane to the central nervous system after oral administration has not been investigated, but is likely to be similar to that following inhalation exposure. YES In an oral study of rats and mice, however, a significant concentration of 1,1,1-trichloroethane or its metabolites was found in the liver, a possible target organ (RTI 1987). Data from dermal studies indicate only that concentrated 1,1,1-trichloroethane is a skin irritant (Duprat et al. 1976; Stewart and Dodd 1964; Torkelson et al. 1958; Wahlberg 1984a, 1984b). Pharmacokinetic data based on dermal exposures are limited; however,

1,1,1-trichloroethane is absorbed following dermal exposure (Fukabori et al. 1977; Kezic et al. 2000, 2001; Stewart and Dodd 1964; Tsuruta 1975). Therefore, the central nervous system and the liver are likely to be target organs after sufficient dermal exposure, although doses required to produce effects would be difficult to predict. Data from inhalation studies in humans were sufficient to derive an acute-duration inhalation MRL based on decreased psychomotor performance (Mackay et al. 1987). An acute-duration oral MRL was not derived due to lack of adequate data.

in animals?

Populations near hazardous waste sites might be exposed to 1,1,1-trichloroethane for brief periods. 1,1,1-Trichloroethane is a frequent contaminant of drinking water supplies, although doses of 1,1,1-trichloroethane ingested by persons living near waste sites are generally significantly lower than doses shown experimentally to cause central nervous system depression or cardiac arrhythmias. Nevertheless, valuable information could be gathered from acute oral toxicity studies with neurological and cardiovascular end points. Similarly, acute dermal studies have focused on death and skin irritation, but have not determined the doses that might produce other effects. This information might be useful because dermal exposure to 1,1,1-trichloroethane is common among workers in certain industries, including those who clean up toxic waste sites. However, human exposure, orally or dermally is likely to be much lower than in acute oral or dermal studies in animals. So such studies may not be necessary.

Intermediate-Duration Exposure. No studies were located regarding intermediate-duration exposure to 1,1,1-trichloroethane in humans. Data from animal studies indicate that the primary target organs of 1,1,1-trichloroethane after intermediate-duration inhalation exposure are the central nervous system and the liver. Behavioral effects, decreased activity, and unconsciousness have been reported in animals (Mattsson et al. 1993; Moser et al. 1985; Torkelson et al. 1958), as have chemical changes indicative of physical damage to the brain (Rosengren et al. 1985). Mild hepatic effects such as increased liver weight and fatty changes also have been reported (Adams et al. 1950; Calhoun et al. 1981; McNutt et al. 1975; Torkelson et al. 1958). Liver necrosis was reported in one study (McNutt et al. 1975). Decreased body weight gain was reported in several studies (Adams et al. 1950; Bruckner et al. 2001; NTP 2000; Prendergast et al. 1967). Reproductive and developmental effects also have been investigated following oral exposure (George et al. 1989; Lane et al. 1982; NTP 1988a, 1988b). Intermediate-duration dermal exposure studies revealed only mild hepatic effects and skin irritation (Torkelson et al. 1958; Viola et al. 1981). Pharmacokinetic data to help identify potential target organs after dermal exposure were not located.

Inhalation data were sufficient to derive an intermediate MRL based on chemical changes suggesting physical damage in the brain of gerbils (Rosengren et al. 1985). Data from the oral study of NTP (2000) were sufficient to derive an acute-duration oral MRL based on reduced body weight gain in female mice. Additional intermediate-duration oral studies could be designed to assess more subtle neurological effects in animals exposed to 1,1,1-trichloroethane via the oral exposure route. Intermediate-duration dermal studies that attempt to determine NOAEL and LOAEL values for systemic and other neurological effects would be valuable, because populations near hazardous waste sites might be exposed to 1,1,1-trichloroethane by this route for intermediate periods. – this seems reasonable

Chronic-Duration Exposure and Cancer. The information provided in the limited number of chronic-duration exposure studies in humans is insufficient to define threshold effect levels. Chronic-duration inhalation and oral studies in animals have not defined threshold effect levels for most end points, although LOAEL values were reported for decreased body weight in rats and mice (Maltoni et al. 1986; NCI 1977; Quast et al. 1988). No studies of chronic-duration dermal exposure in humans or animals were located. Pharmacokinetic studies after acute oral exposure indicate that the liver is a potential target organ; the mild liver effects observed in chronic-duration animal studies are supportive (Quast et al. 1988). Existing pharmacokinetic data, however, are not sufficient to identify other target organs after chronic oral, inhalation, or dermal exposure, even though relatively high exposure levels have been tested.

MRL values were not derived for chronic-duration inhalation exposure studies because target organs could not be identified. Similarly, a chronic oral MRL was not derived due to lack of adequate data.

Because populations near hazardous waste sites might be chronically exposed to 1,1,1-trichloroethane, studies that attempt to determine threshold effect levels for inhalation, oral, and dermal exposure would be valuable. – yes

Two-year cancer bioassays have been performed following both inhalation and oral exposure. The results of one oral study indicate that 1,1,1-trichloroethane may have increased the occurrence of immunoblastic lymphosarcoma in rats (Maltoni et al. 1986). Definite conclusions or implications could not be drawn based on this report, however, since experimental procedures were compromised, only one dose level was used and only a small number of rats responded. Although no effects were found in a well-designed inhalation study at exposure levels ≤1,500 ppm (Quast et al. 1988), a follow-up chronic inhalation

bioassay incorporating higher doses, an oral bioassay using several dose levels, larger study groups, and use of more than one species would allow more definitive assessment of 1,1,1-trichloroethane's carcinogenic potential. (probably not necessary. This compound has weak mutagenic activity, no evidence of promoter activity. Human exposure probably too low to be concerned about carcinogenic effects.

Genotoxicity. No studies were located regarding the genotoxic potential of 1,1,1-trichloroethane in humans. Existing genotoxicity studies indicate that 1,1,1-trichloroethane may be weakly mutagenic in *Salmonella* (Gocke et al. 1981; Nestmann et al. 1980, 1984; Simmon et al. 1977) and is able to induce deletions via intrachromosomal recombination in the yeast *Saccharomyces cerevisiae* (Brennan and Schiestl 1998) and transform mammalian cells *in vitro* (Daniel and Dehnel 1981; Hatch et al. 1982, 1983; Milman et al. 1988; Price et al. 1978; Tu et al. 1985). Numerous tests of other genotoxic effects have mostly been negative; however, only a few of these studies made an effort to prevent loss of 1,1,1-trichloroethane due to volatility. Studies designed to account for this property would allow a more complete assessment of genotoxicity. Valuable information also would be provided by tests of chromosomal aberrations in peripheral lymphocytes from humans known to have been exposed to 1,1,1-trichloroethane.

probably worthwhile – how will you attribute CA to 1,1,2-TCA?

Reproductive Toxicity. An epidemiology study found no relationship between adverse pregnancy outcomes and occupational exposure of fathers to 1,1,1-trichloroethane during spermatogenesis (Taskinen et al. 1989). Limited information regarding reproductive toxicity in animals was located. A multigeneration reproduction study of rats exposed to 1,1,1-trichloroethane in drinking water found no reproductive effects (Lane et al. 1982). Histological evaluation of reproductive organs and tissues after inhalation exposure of rats and mice revealed no lesions attributable to 1,1,1-trichloroethane exposure (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977). However, testicular degeneration was observed in guinea pigs (Adams et al. 1950). Reduced epididymal spermatozoal concentration was noted in male rats and mice administered 1,1,1-trichloroethane in the diet at a concentration of 80,000 ppm (approximate doses of 4,800 and 15,000 mg/kg/day) for 13 weeks, but there were no other indications of adverse male reproductive effects and no signs of altered estrus in similarly-treated female rats and mice (NTP 2000). There are no pharmacokinetic data in humans to help evaluate potential reproductive effects. Reproductive function has not been assessed in animals after inhalation or dermal exposure to 1,1,1-trichloroethane; however, available toxicokinetic data do not suggest route-specific target organs. Nevertheless, an inhalation study of reproductive function in animals would be valuable for assessing reproductive toxicity, since that is the predominant route of exposure for humans to 1,1,1-trichloroethane. yes

Developmental Toxicity. No relationship between maternal exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes (spontaneous abortions/congenital malformations) was found in human epidemiology studies (Deane et al. 1989; Lindbohm et al. 1990; Swan et al. 1989; Taskinen et al. 1989; Windham et al. 1991; Wrensch et al. 1990a, 1990b). Some studies in animals indicate that 1,1,1-trichloroethane is a potential developmental toxicant in quite high doses. Minor skeletal anomalies (delayed ossification and extra ribs in rats and rabbits, respectively, and decreased fetal body weight in rats) have been reported after inhalation exposure of pregnant rats or rabbits during major organogenesis (BRRC 1987a, 1987b; York et al. 1982). These exposures were at concentrations that also produced significant maternal toxicity in two of the studies (BRRC 1987a, 1987b). Delays in developmental milestones (pinnae detachment, incisor eruption, and eye opening) and impaired performance in neurobehavior tests were noted in mouse pups of dams exposed to 1,1,1-trichloroethane during later stages of gestation at levels that did not result in apparent maternal toxicity (Jones et al. 1996). No neurological effects were reported in the offspring of rats gavaged with 1,1,1-trichloroethane during gestation and lactation (Dow Chemical 1993). A multigeneration developmental study of oral 1,1,1-trichloroethane exposure reported no teratogenic effects in rats (Lane et al. 1982). Although developmental studies by the dermal route are lacking, available pharmacokinetic data do not suggest route-specific target organs. Furthermore, valuable information can be obtained by using the existing physiologically-based pharmacokinetic models once these are validated by comparison with 1,1,1-trichloroethane levels measured over time in different tissues for the different exposure routes.

Immunotoxicity. No studies were located regarding the immunotoxicity of 1,1,1-trichloroethane in humans. Information regarding the lymphoreticular system was limited to reports of spleen congestion in subjects acutely exposed to high levels of 1,1,1-trichloroethane (Gresham and Treip 1983; Stahl et al. 1969). Exposed mice were not more susceptible to bacterial infection than unexposed control mice after a single inhalation exposure to 1,1,1-trichloroethane (Aranyi et al. 1986). Very limited information exists regarding histology and function of tissues of the lymphoreticular system after 1,1,1-trichloroethane exposure by any route. Histological evaluation of lymphoreticular tissues, including lymph nodes, thymus, and spleen, revealed no lesions attributable to 1,1,1-trichloroethane exposure (Adams et al. 1950; Calhoun et al. 1981; Kjellstrand et al. 1985b; Prendergast et al. 1967; Torkelson et al. 1958).

An acute- or intermediate-duration exposure study including a comprehensive evaluation of lymphoid tissues and blood components would provide valuable information regarding potential immunotoxicity. ?

— probably could get info. from a rather small study.

Neurotoxicity. The central nervous system is apparently the primary target organ of 1,1,1-trichloroethane toxicity. Behavioral effects, altered EEG recordings, ataxia, unconsciousness, and death have been reported in human and animal studies (Halogenated Solvents Industry Alliance 1991; Balster et al. 1982, 1997; Bowen and Balster 1996, 1998; Bruckner et al. 2001; Clark and Tinston 1982; DeCeaurriz et al. 1983; del Amo et al. 1996; Dornette and Jones 1960; Evans and Belster 1993; Gamberale and Hultengren 1973; Garnier et al. 1991; Gehring 1968; Kelafant et al. 1994; Mackay et al. 1987; Mattsson et al. 1993; Moser and Balster 1985, 1986; Muttray et al. 2000; Páez-Martínez et al. 2003; Spencer et al. 1990; Stewart et al. 1961, 1969; Sullivan 1994; Torkelson et al. 1958; Warren et al. 1997, 1998; Wiley et al. 2002; Winek et al. 1997; Woolverton and Balster 1981; You et al. 1994). Neurochemical changes following prolonged inhalation exposure, suggesting morphological damage to the brain, have been reported in gerbils (Rosengren et al. 1985). Respiratory depression appears to cause death in humans and animals. Most studies were conducted by inhalation exposure, but limited data on oral exposure were also available, including a recent study in which no neurological effects were reported in the offspring of rats treated during gestation and lactation (Dow Chemical 1993) (see Developmental Toxicity). Neurological effects have not been reported after dermal exposure.

should be done

Additional in-depth studies of the effects of 1,1,1-trichloroethane on neurological structure and function might provide important information regarding the mechanisms and reversibility of 1,1,1-trichloroethane-induced neurological dysfunction. Studies to follow-up on the reported changes in GFA protein following 1,1,1-trichloroethane exposure may be helpful. Acute-, intermediate-, and chronic-duration exposure studies by the oral route, including comprehensive histological evaluations and nervous system function tests, would provide information regarding the dose-response relationship for this route of exposure. An acute-duration dermal exposure to assess the potential for neurotoxicity by this route would also be useful, although toxicokinetic data available do not suggest route-specific target organs. Populations residing near hazardous waste sites or in occupational settings might be exposed to 1,1,1-trichloroethane. Well-designed and controlled epidemiology studies of these populations may provide useful information on the potential for 1,1,1-trichloroethane at relevant exposure levels to produce neurological disturbances in humans. Would have to have a significant no. of humans exposed predominately to TCE to produce definitive results.

Epidemiological and Human Dosimetry Studies. Epidemiology studies have investigated the relationship between long-term exposure to 1,1,1-trichloroethane and systemic, neurological, reproductive, developmental, and cancer effects in humans, but no health effects associated with exposure have been reported. These studies, however, are limited in design and scope and do not provide definitive

conclusions regarding the health effects of 1,1,1-trichloroethane exposure. More extensive studies might provide a definitive assessment of the health hazards of chronic 1,1,1-trichloroethane exposure in humans, especially for occupationally exposed populations. If such effects are identified, human dosimetry studies may be able to correlate 1,1,1-trichloroethane levels in human tissues or fluids with chronic health effects. must be done carefully! The usefulness of such studies on individuals living near hazardous waste sites is questionable since exposure is relatively low and the half-life of 1,1,1-trichloroethane and its metabolites too short. Acute experimental studies in humans have established inhalation exposure levels associated with acute neurological effects. Subpopulations potentially exposed to 1,1,1-trichloroethane include people residing near hazardous waste sites where the chemical is stored, people who encounter it in the workplace (either in its manufacture or application), and people who use household products that contain it. It should be mentioned, however, that as a result of Title VI of the Clean Air Act, potential human exposure to 1,1,1-trichloroethane is expected to be gradually reduced (see Chapter 6). so, is this necessary?

Biomarkers of Exposure and Effect.

Exposure. Known biomarkers of 1,1,1-trichloroethane exposure include blood, breath, and urine levels of the chemical and its two major metabolites, trichloroethanol and trichloroacetic acid. Metabolism of trichloroethylene and perchloroethylene also produces trichloroethanol and trichloroacetic acid; therefore, these metabolites are not unique to 1,1,1-trichloroethane (Monster 1988). Environmental 1,1,1-trichloroethane levels are significantly correlated with the levels in blood, breath, and urine (Hartwell et al. 1987a; Mizunuma et al. 1995; Monster 1986; Wallace et al. 1982, 1984b, 1985, 1987a, 1987b, 1987c). 1,1,1-Trichloroethane is rapidly cleared from the body after exposure (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984; Stewart et al. 1961). The two metabolites have a much longer half-life in the body than the parent compound. Therefore, 1,1,1-trichloroethane levels in the blood, breath, and urine may be used as biomarkers only if they are measured during or shortly after exposure. The two metabolites are more useful as biomarkers for a somewhat longer period after exposure. Because 1,1,1-trichloroethane's half-life in the body is short, and because hematological profiles and clinical chemistry parameters are not usually affected, the further development of biomarkers based on easily-obtained biological fluids may not be useful. agree

Effect. No specific biomarkers of effect for 1,1,1-trichloroethane were located in the literature. The central nervous system is apparently the most sensitive organ in humans and animals, and neurotoxicity (decreased psychomotor performance, ataxia, and unconsciousness) is observed after short-term high-

level exposure. Development of specific biomarkers of effect would facilitate medical surveillance, which could lead to early detection of adverse effects.

Absorption, Distribution, Metabolism, and Excretion. The absorption, metabolism, and elimination of 1,1,1-trichloroethane have been studied extensively in humans and animals. Distribution has not been as well studied. 1,1,1-Trichloroethane is rapidly and efficiently absorbed by the lung, skin (under conditions to prevent evaporation), and gastrointestinal tract of humans and animals (Astrand et al. 1973; Fukabori et al. 1977; Kezic et al. 2000, 2001; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; RTI 1987; Stewart and Andrews 1966; Stewart and Dodd 1964; Tsuruta 1975). As duration of inhalation exposure increases in humans and animals, the percentage net absorption decreases, because steady-state levels are approached in the blood and tissues, and 1,1,1-trichloroethane is metabolized at a low rate. A study with humans equipped with respirators indicated that, during exposure to 1,1,1-trichloroethane vapors in the atmosphere, absorbed doses from inhaled 1,1,1-trichloroethane are much larger than doses from dermal absorption (Riihimaki and Pfaffli 1978). Animal studies demonstrated that, once absorbed, 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, including developing fetuses, with preferential distribution to fatty tissues (Holmberg et al. 1977; Katagiri et al. 1997; Schumann et al. 1982a; Takahara 1986b). Human data regarding the compound's distribution are limited to the observation that detectable levels were found in subcutaneous fat, kidney fat, liver, lung, and muscle in 30 autopsy cases (Alles et al. 1988). The predominant pathway of 1,1,1-trichloroethane elimination by humans and animals, regardless of exposure route, is exhalation of the unchanged compound (Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; RTI 1987; Schumann et al. 1982a, 1982b). When exposure ceases, the compound rapidly clears from the body. Only trace amounts of the compound remained in animal tissues within days of short-term exposure. Further studies in humans regarding extent and rates of absorption and elimination with dermal exposure to aqueous 1,1,1-trichloroethane solutions or suspensions under conditions allowing evaporation from the skin may provide useful information on dermal contact with contaminated water.

this is actually pretty extensive data!

Probably not necessary

Experiments with animals and humans have demonstrated that only small fractions of absorbed 1,1,1-trichloroethane doses (<10%) are metabolized, regardless of the exposure route (Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Schumann et al. 1982a, 1982b). 1,1,1-Trichloroethane is metabolized oxidatively to trichloroethanol and trichloroacetic acid by a concentration-dependent, saturable process that appears to involve the cytochrome P-450 mixed-function oxidase system. These metabolites have been detected in urine excreted from exposed humans and animals; other minor

metabolites (CO_2 and acetylene, the latter formed by the reductive dechlorination of 1,1,1-trichloroethane under conditions of low oxygen supply) are eliminated in expired air.

The hepatotoxicity of 1,1,1-trichloroethane is quite low compared to other chlorinated hydrocarbons, including 1,1,2-trichloroethane. The relatively low toxicity of 1,1,1-trichloroethane may be due to its relatively low metabolism rate, since the more hepatotoxic halocarbons are extensively metabolized. Whether the mild effects of repeated 1,1,1-trichloroethane exposure are evoked by the parent compound or the limited quantities of metabolites produced is not known, however. The available data indicate that the acute effects on the central nervous and the cardiovascular system are caused by 1,1,1-trichloroethane and not its metabolites. The interference of 1,1,1-trichloroethane with membrane-mediated processes, due to lipophilicity, may be responsible for the acute effects on these systems; several cellular and biochemical processes appear to be affected by 1,1,1-trichloroethane.

Comparative Toxicokinetics. The toxicokinetic pattern of 1,1,1-trichloroethane is qualitatively similar in humans, rats, and mice. There are major quantitative differences, however, including a higher blood:air partition coefficient, higher respiratory and circulatory rates, and increased rate of metabolism in mice. This comparison has led to a suggestion that rats may be a better model for humans than mice. Physiologically-based pharmacokinetic models have been developed to describe the kinetic behavior of 1,1,1-trichloroethane in mice, rats, and humans; these models have been used to make interspecies and interroute extrapolations in estimating 1,1,1-trichloroethane exposure levels in humans that will produce (or not produce) toxic effects (Bogen and Hall 1989; Dallas et al. 1989; Dobrev et al. 2001, 2002; Leung 1992; Nolan et al. 1984; Poet et al. 2000; Reitz et al. 1988; USAF 1990). Further research verifying the metabolic constants and other input parameters (partition coefficients, tissue values and blood flows, cardiac output, and respiratory volumes) used in these models might improve the accuracy and utility of the models in interspecies extrapolations.

Methods for Reducing Toxic Effects. Suggested methods to treat the effects of acute exposure to 1,1,1-trichloroethane and other halogenated hydrocarbons are generally supportive and rely on the body's ability to eliminate rapidly 1,1,1-trichloroethane and its metabolites. Animal studies indicate that intravenous injection or infusion of calcium gluconate or phenylephrine are protective against acute blood pressure reduction caused by exposure to 1,1,1-trichloroethane (Herd et al. 1974). Further animal testing is needed to assess whether these compounds might be used to resuscitate individuals exposed to high concentrations of 1,1,1-trichloroethane.

Children's Susceptibility. No information was located regarding potential age-related differences in susceptibility to 1,1,1-trichloroethane in humans. Delays in developmental milestones and impaired performance in neurobehavior tests in mouse pups of dams exposed to 1,1,1-trichloroethane during later stages of gestation (Jones et al. 1996) indicate that developing organisms may be more susceptible than adults to the toxic effects of 1,1,1-trichloroethane. Additional well-designed animal studies should be performed to adequately assess the potential for age-related increased susceptibility to 1,1,1-trichloroethane. Actually, the existing database is probably adequate.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Two ongoing studies pertaining to 1,1,1-trichloroethane were located in a search of the Federal Research in Progress database (FEDRIP 2004).

Dr. S. Bowen of Wayne State University in Detroit, Michigan has designed experiments to characterize subjective and psychomotor effects of toluene and 1,1,1-trichloroethane. The research includes comparison of the results with those of other abused inhalants. Other experiments are designed to elucidate basic mechanisms underlying and controlling inhalant abuse.

Dr J. Zacny of the University of Chicago, Chicago, Illinois is developing a human laboratory model of inhalant abuse by studying potential determinants of abuse liability of inhalants (including 1,1,1-trichloroethane) in healthy volunteers.

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

5.1 PRODUCTION

are they still producing it? – given the 2002 mandate?

Two chemical companies are listed as domestic manufacturers in 2003 (SRI 2003): Vulcan Materials Co. Chemicals Division in Geismer, Louisiana and PPG Industries in Lake Charles, Louisiana. The estimated total production capacity at each of the facilities in 1994 (in millions of pounds) is 350 for PPG's plant in Lake Charles, Louisiana and 160 for Vulcan's plant in Geismar, Louisiana (estimated total capacity of 510 million pounds as of April 1, 2003) (SRI 2003).

The total production volumes of 1,1,1-trichloroethane fell from 720 million pounds in 1992 to 450 million pounds in 1993 (CMR 1995). The demand for 1,1,1-trichloroethane was projected to decline at the rate of -10% per year through 1999 (CMR 1995). According to the 1990 amendments to the Clean Air Act and the Montreal Protocol, U.S. production of 1,1,1-trichloroethane will be cut incrementally until the proposed phase-out scheduled to occur by January 2002 (EPA 2004m). During the period beginning on January 1, 2002 and ending on January 1, 2005, production of limited amounts of 1,1,1-trichloroethane may be authorized by the Administrator for use in essential applications. Despite the proposed phase-out, 1,1,1-trichloroethane was still being manufactured in the United States in 2002 in a production volume range of >100 to <500 million pounds for 2002 (Inventory Update Rule 2004).

Besides the above producers of 1,1,1-trichloroethane, Table 5-1 reports the number of facilities in each state that manufacture and process 1,1,1-trichloroethane, the intended use of the product, and the range of maximum amounts of 1,1,1-trichloroethane stored on site. The data reported in Table 5-1 are derived from the Toxics Release Inventory (TRI) (TRI01 2004). Only certain types of facilities were required to report to the TRI databank of EPA. Hence, this is not an exhaustive list.

The most common method for industrial preparation of 1,1,1-trichloroethane is the reaction of hydrochloric acid with vinyl chloride (obtained from 1,2-dichloroethane) to obtain 1,1-dichloroethane, followed by either thermal or photochemical chlorination. Other methods include the catalyzed addition of hydrogen chloride to 1,1-dichloroethylene, and the direct chlorination of ethane itself, followed by separation from the other products produced (Archer 1979). Commercial grades of 1,1,1-trichloroethane

* Administrator of EPA? ADSTR?

usually contain some inhibitor, such as nitromethane, methyl ethyl ketone, toluene, 1,4-dioxane, butylene oxide, 1,3-dioxolane, or secondary butyl alcohols (Archer 1979; OHM/TADS 1992).

5.2 IMPORT/EXPORT

According to the Commerce Department's National Trade Data Bank (NTDB 1994), the following amounts of 1,1,1-trichloroethane (in pounds with kg in parentheses) were exported from the United States during the period 1989–1993: 124.3 million (56.4 million) in 1989; 114.6 million (52.0 million) in 1990; 162.4 million (73.7 million) in 1991; 139.7 million (63.4 million) in 1992; and 75.8 million (34.4 million) in 1993. The amount of 1,1,1-trichloroethane exported has declined since 1991. Because 1,1,1-trichloroethane may be an ozone-destroying chemical, its export and import will continue to decline in future years as a result of the Montreal Protocol. No recent data were found regarding the import and export of 1,1,1-trichloroethane in the United States.

5.3 USE

1,1,1-Trichloroethane was developed initially as a safer solvent to replace other chlorinated and flammable solvents. The uses of 1,1,1-trichloroethane as of 1995 and percentages of total amount devoted to each use are: hydrochlorofluorocarbon (HCFC) intermediate (60%), vapor degreasing and cold cleaning 25% (through 1995), adhesives 5%, coatings and inks 3%, textiles 2%, and electronics and miscellaneous 5% (CMR 1995). During the period beginning on January 1, 2002 and ending on January 1, 2005, the Administrator may authorize the use of limited amounts of 1,1,1-trichloroethane for essential applications such as medical devices and aviation safety. An example is its use for nondestructive testing for metal fatigue and corrosion of existing airplane engines and airplane parts susceptible to metal fatigue. These applications have no safe and effective substitute available. Probably going to have to develop a substitute before complete cessation of TCE production.

1,1,1-Trichloroethane was used as a solvent for adhesives (including food packaging adhesives) and in metal degreasing, pesticides, textile processing, cutting fluids, aerosols, lubricants, cutting oil formulations, drain cleaners, shoe polishes, spot cleaners, printing inks, and stain repellents, among other uses. It was used in industry primarily for cold-cleaning, dip cleaning, bucket cleaning, and vapor degreasing operations of items such as precision instruments, molds, electrical equipment, motors, electronic components and instruments, missile hardware, paint masks, photographic film, printed circuit

boards, generators, switchgears, semiconductors, high vacuum equipment, fabrics, and wigs. It was also used for on-site cleaning of printing presses, food packaging machinery, and molds. 1,1,1-Trichloroethane is also used as a chemical intermediate in the production of hydrofluorocarbons and vinyl chloride. It was formerly used as a food and grain fumigant (Archer 1979; Aviado et al. 1976, 1980; Budavari 1989; Sax and Lewis 1987; Stewart 1983; WHO 1992). Probably didn't cause problems due to rapid volatility in air.

1,1,1-Trichloroethane was used extensively in household products. In a "shopping basket" survey, 1,1,1-trichloroethane was found in 216 of 1,159 common household products chosen as likely to contain solvents at concentrations >0.1% by weight (Sack et al. 1992). In a similar study, 1,1,1-trichloroethane was found in 32 of 67 categories (1,026 brands sampled) of common household products at concentrations >1% by weight; trace amounts were listed in all 67 categories (EPA 1987; Maklan et al. 1987). Some of the several commonly used household items that may contain 1,1,1-trichloroethane are shown in Table 5-2. 1,1,1-Trichloroethane is emitted during use of items prevalent in the average home (Pleil and Whiton 1990; Wallace et al. 1987b).

5.4 DISPOSAL

1,1,1-Trichloroethane has been identified as a hazardous waste by EPA, and disposal of this waste is regulated under the Federal Resource Conservation and Recovery Act (RCRA). Specific information regarding federal regulations on 1,1,1-trichloroethane disposal on land, in municipal solid waste landfills, in incinerators, and during underground injection is available in the Code of Federal Regulations (EPA 1992a, 1992b, 1992c, 1992d). Disposal of 1,1,1-trichloroethane can be accomplished through its destruction in a high temperature incinerator equipped with a hydrochloric acid scrubber. The destruction and removal efficiency (DRE) for 1,1,1-trichloroethane in hazardous wastes must attain 99.99% (Carroll et al. 1992). Potential methods of incineration include liquid injection, rotary kiln, and fluidized bed incineration (Carroll et al. 1992; HSDB 2004). Product residues and sorbent media may be packaged in a 17H epoxy-lined drum, encapsulated in an organic polyester resin, and disposed of at an approved EPA disposal site (OHM/TADS 1992). Other methods that have shown promise for the destruction of 1,1,1-trichloroethane are homogeneous sonochemical treatment for aqueous wastes (Cheung et al. 1991) and a combination of ozonation and ultraviolet treatment for groundwater (Kusakabe et al. 1991). From a laboratory feasibility study, it was concluded that the in situ biodegradation of 1,1,1-trichloroethane in soils by methane-oxidizing bacteria was not a viable bioremediation method (Broholm et al. 1991).

Sonochemical treatment would seem preferable to this.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

1,1,1-Trichloroethane has been identified in at least 809 of the 1,647 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). However, the number of sites evaluated for 1,1,1-trichloroethane is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 804 are located within the United States, 3 are located in the Commonwealth of Puerto Rico (not shown), 1 is located in the Virgin Islands (not shown), and 1 is located in Guam (not shown).

still is?

1,1,1-Trichloroethane is a synthetic compound that was released to the environment by human industrial activity. It was released to the environment by process and fugitive emissions during its manufacture, formulation, and use in both consumer and industrial products. Because 1,1,1-trichloroethane is volatile and was used as a solvent in many products, it was most frequently found in the atmosphere due to volatilization during production and use. Under the Clean Air Act as amended in 1990, all production and use of 1,1,1-trichloroethane was scheduled to cease as of January 1, 2002. 1,1,1-Trichloroethaene may still be used for essential applications such as medical devices and aviation safety (for the testing of metal fatigue and corrosion of existing airplane engines and other parts susceptible to corrosion) until January 1, 2005. Despite the proposed phase-out, 1,1,1-trichloroethane was still being manufactured in the United States in 2002 in a production volume range of >100–<500 million pounds. More current production data are not yet available and therefore, it is unclear what stage the phase-out is in at this time.

presumably far more than is required for medical devices & aviation safety

1,1,1-Trichloroethane is no longer used in common household products. The current likelihood of the exposure of general population to 1,1,1-trichloroethane is remote. Possible routes of exposure to 1,1,1-trichloroethane were inhalation, dermal contact, or through the ingestion of either contaminated water or food. Exposure by inhalation was expected to predominate. The general population was exposed to 1,1,1-trichloroethane because of its prevalence in common household products. Indoor air concentrations were determined to be greater than nearby outdoor concentrations, probably as a result of its presence in a myriad of consumer products in the past. Occupational exposure to 1,1,1-trichloroethane could occur by inhalation or dermal contact during its manufacture and formulation, during its use as a cleaner of manufactured components, and during the application of the numerous paints, resins,

adhesives, and cleaners containing it as a solvent. At hazardous waste sites, inhalation is expected to be the predominant route of exposure; however, ingestion of contaminated water may occur also.

The dominant environmental fate process for 1,1,1-trichloroethane is volatilization to the atmosphere. Once in the atmosphere, reaction with photochemically-produced hydroxyl radicals is expected to be the most important transformation process for 1,1,1-trichloroethane; the estimated atmospheric lifetime for this process is about 6 years. This long atmospheric lifetime allows about 15% of 1,1,1-trichloroethane to migrate to the stratosphere, where it may be degraded by lower wavelength ultraviolet light, not available in the troposphere, to produce atomic chlorine. The chlorine atoms produced in the stratosphere by this process may react with ozone causing the erosion of the ozone layer. However, direct photochemical degradation of 1,1,1-trichloroethane in the troposphere should not occur. The moderate water solubility of 1,1,1-trichloroethane suggests that rain washout can occur; however, 1,1,1-trichloroethane removed from the atmosphere by this process would be expected to re-volatilize. The lengthy half-life for 1,1,1-trichloroethane in the troposphere allows it to be carried great distances from its original point of release, and it has been found in remote places far from any known source of release.

If released to soil, 1,1,1-trichloroethane should display high mobility and the potential for leaching into groundwater. Volatilization from soil surfaces to the atmosphere is expected to be an important fate process. Although data regarding biodegradation of 1,1,1-trichloroethane in soil are lacking, it is not expected to be an important fate process. 1,1,1-Trichloroethane is not expected to undergo aerobic biodegradation, but there is some experimental evidence that biodegradation may occur under anaerobic conditions.

Once released to surface water, 1,1,1-trichloroethane is expected to undergo volatilization to the atmosphere. Neither adsorption to sediment nor bioconcentration in aquatic organisms is recognized as an important removal process. Aerobic biodegradation of 1,1,1-trichloroethane can occur in the presence of methane-oxidizing bacteria. If released to groundwater, biodegradation of 1,1,1-trichloroethane under anaerobic conditions is known to occur; however, it appears to be a slow process under most environmental conditions.

1,1,1-Trichloroethane may very slowly undergo abiotic degradation in soil or water by elimination of hydrochloric acid (HCl) to form 1,1-dichloroethene, which also can be considered a pollutant, or it can

undergo hydrolysis to form the naturally occurring acetic acid. Direct photochemical degradation is not expected to be an important fate process.

6.2 RELEASES TO THE ENVIRONMENT

The manufacture and use of 1,1,1-trichloroethane was scheduled to be phased out by 2002. Since the declines in emissions closely follow the declines in production and use, the emissions of 1,1,1-trichloroethane to the atmosphere should show a corresponding decline (EPA 2004m).

6.2.1 Air

A correlation of data from the EPA Air Toxics Emission Inventory with industrial source codes (SIC codes), shows that volatile emissions of 1,1,1-trichloroethane are associated with 122 different industrial classifications that run the gamut from manufacturing and formulation to secondary uses (Pacific Environmental Services, Inc. 1987). Release of 1,1,1-trichloroethane, in most cases, was an expected result of its use (Spence and Hanst 1978). Small amounts of 1,1,1-trichloroethane was also released to the atmosphere from coal-fired power plants (Garcia et al. 1992), from incineration of hospital wastes (Green et al. 1992; Walker and Cooper 1992), incineration of military nerve agents (Mart and Henke 1992), incineration of industrial wastes containing certain plastics and waste solvents (Nishikawa et al. 1992, 1993), and incineration of municipal waste water sludge (Vancil et al. 1991). 1,1,1-Trichloroethane contained in consumer products was released into the atmosphere during the application, drying, or curing of these products. 1,1,1-Trichloroethane could enter the atmosphere via the air-stripping treatment of waste water. Volatilization, which accounts for ≈100% of removal in waste water, occurs during this process (Kincannon et al. 1983a). Volatilization from waste lagoons is also likely (Shen 1982).

Precise quantitative data on 1,1,1-trichloroethane air emissions are lacking. A large proportion of total production probably found its way into the atmosphere. Estimates for 1984 suggest that 100.4 kilotons (220 million pounds) were released during use by the European Economic Community (EEC) and other western European countries, a figure representing some 70% of total consumption in Europe (Herbert et al. 1986). Global estimates indicate that 1,497 million pounds (679 million kg) of 1,1,1-trichloroethane were released to the atmosphere in 1988 (Midgley 1989). 1,1,1-Trichloroethane releases in air from facilities in each state in the United States that manufactured or processed 1,1,1-trichloroethane during

2001 are reported in the Toxics Release Inventory (TRI) and listed in Table 6-1 (TRI01 2004). According to TRI01 (2004), an estimated total of 206,859 pounds of 1,1,1-trichloroethane, amounting to 98.4% of the total environmental release, was discharged to the air from manufacturing and processing facilities in the United States in 2001. **The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.** However, a comparison of TRI data for 1992 and 2001 (115 million pounds and 206,859 pounds, respectively) shows that the nationwide emission of 1,1,1-trichloroethane in the atmosphere has decreased by 99.8% during this period. A 36% reduction in atmospheric emissions was observed in Irvine, California, from 1989 to 1990 (Brown and Hart 1992). Most processes that use 1,1,1-trichloroethane result in some fugitive emissions. For example, the release of 1,1,1-trichloroethane from an industrial solvent recycling facility was 16.7% of the throughput (Balfour et al. 1985).

6.2.2 Water

1,1,1-Trichloroethane can be released to surface water from the waste water of industries in any of the numerous industrial classifications that used or produced this compound. The STORET database for values registered in the years 1980–1988 shows that 1,1,1-trichloroethane tested positive in 12% of effluent samples with maximum, median, and mean concentrations of 6,500, 8.0, and 171 mg/L, respectively (STORET 1988). 1,1,1-Trichloroethane releases in water, including release to publicly owned treatment works (POTW), from facilities in each state in the United States that manufactured or processed 1,1,1-trichloroethane during 2001 are reported in Table 6-1 (TRI01 2004). According to TRI01 (2004), 0.01% of the total 1,1,1-trichloroethane environmental release was discharged to environmental waters from manufacturing and processing facilities in the United States in 2001. **The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.** Higher concentrations of 1,1,1-trichloroethane have been found in surface waters near known industrial sources, such as effluent outfalls or disposal sites, compared to the levels found upstream from these sources (see Table 6-2) (Dreisch et al. 1980; Hall 1984; Kaiser and Comba 1986; Kaiser et al. 1983; Wakeham et al. 1983a).

1,1,1-Trichloroethane has been found in samples from four U.S. cities measured in the National Urban Runoff Program (Cole et al. 1984). 1,1,1-Trichloroethane has been found in the effluent from water treatment plants and municipal waste water (Comba and Kaiser 1985; Corsi et al. 1987; DeWees et al.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

1,1,1-Trichloroethane is a volatile organic compound with moderate water solubility (1,500 mg/L at 25 °C) (Horvath 1982). The experimental Henry's law constants measured for this compound range from 6.3×10^{-3} to 17.2×10^{-3} atm m^3/mol at 25 °C (Chiou et al. 1980; Gossett 1987; Tse et al. 1992); this suggests that volatilization from water should be the dominant fate process. Volatilization of 1,1,1-trichloroethane from water has readily occurred in the laboratory, in the field, and during waste water treatment (Dilling 1977; Dilling et al. 1975; Kincannon et al. 1983b; Piwoni et al. 1986; Wakeham et al. 1983b). Volatilization of 1,1,1-trichloroethane also has occurred from soil and from the groundwater of unconfined aquifers to the soil (Kreamer 1984; Piwoni et al. 1986).

Based on the experimental values for the log octanol/water partition coefficient (K_{ow}), 2.49 (Hansch and Leo 1985), and log K_{oc}, in the range of 2.02–2.26 (Chiou et al. 1979; Friesel et al. 1984; Park and Lee 1993), 1,1,1-trichloroethane would be expected to show high mobility in soil and readily leach into groundwater (Lyman et al. 1990; Swann et al. 1983). In surface waters, 1,1,1-trichloroethane would not be expected to show appreciable adsorption to sediment or suspended organic material. An experimental bioconcentration factor (BCF) of 9 (bluegill sunfish) has been determined for 1,1,1-trichloroethane (Barrows et al. 1980), suggesting that in fish and other aquatic organisms, uptake from water should not be an important fate process.

1,1,1-Trichloroethane has a vapor pressure of 123 mm Hg at 20 °C (see Table 4-2), which means that it exists in the vapor phase in the atmosphere (Eisenreich et al. 1983). Since this compound has moderate water solubility (see Table 4-2), vapor phase 1,1,1-trichloroethane will be removed from the air via washout by rain and transported to the terrestrial surface. It has been identified in rainwater (Jung et al. 1992; Kawamura and Kaplan 1983; Pluemacher and Renner 1993; Rasmussen et al. 1983). 1,1,1-Trichloroethane removed by rain water would be expected to re-volatilize rapidly to the atmosphere. Because of its long half-life of ≈4 years in the atmosphere (see Section 6.3.2.1), tropospheric 1,1,1-trichloroethane will be transported to the stratosphere, where it will participate in the destruction of the ozone layer. It will also undergo long-distance transport from its sources of emissions to other remote and rural sites. This is confirmed by the detection of this synthetic chemical in forest areas of Northern and Southern Europe and in remote sites (Ciccioli et al. 1993).

6.3.2 Transformation and Degradation

6.3.2.1 Air

The dominant atmospheric fate process for 1,1,1-trichloroethane is predicted to be degradation by interaction with photochemically-produced hydroxyl radicals. Earlier experimental rate constants for this gas-phase reaction ranged from 2.8×10^{-14} to 1.06×10^{-14} cm^3/mol-sec (20–30 °C) (Butler et al. 1978; Chang and Kaufman 1977; Cox et al. 1976; Crutzen et al. 1978; Howard and Evenson 1976; Jeong et al. 1984). More recent work indicates that this rate constant ranges from 0.95×10^{-14} cm^3/mol-sec to 1.2×10^{-14} cm^3/mol-sec (Finlayson-Pitts et al. 1992; Jiang et al. 1992; Lancar et al. 1993; Talukdar et al. 1992). 1,1,1-Trichloroethane is degraded via H-atom abstraction to CCl_3CH_2 and reacts with O_2 to yield the peroxy radical ($CCl_3CH_2O_2$) (DeMore 1992; Spence and Hanst 1978). Using an estimated atmospheric hydroxyl radical concentration of 5.0×10^5 mol/cm^3 (Atkinson 1985), the more recent rate constants translate to a calculated lifetime or residence time of ≈6 years. The estimated atmospheric lifetime of 1,1,1-trichloroethane which incorporates all removal processes, was also estimated to be ≈6 years (Prinn et al. 1987; Prinn et al. 1992). This indicates that the predominant tropospheric sink of 1,1,1-trichloroethane is through its reaction with OH radicals.

Photolytic degradation experiments have been performed in the presence of NO and NO_2; 1,1,1-trichloroethane underwent <5% degradation in 24 hours in the presence of NO (Dilling et al. 1976). In a smog chamber experiment in the presence of NO_x 1,1,1-trichloroethane showed a disappearance rate of 0.1% per hour (Dimitriades and Joshi 1977). Other studies have also concluded that 1,1,1-trichloroethane has low potential to form ozone as a result of photochemical reaction in the presence of NO_x (Andersson-Skoeld et al. 1992; Derwent and Jenkin 1991).

Under laboratory conditions thought to mimic atmospheric smog conditions, direct photochemical irradiation of 1,1,1-trichloroethane in the presence of elemental chlorine was performed. 1,1,1-Trichloroethane was the least reactive and thus the most stable of all chloroethanes under these conditions (Spence and Hanst 1978).

Direct photochemical degradation of 1,1,1-trichloroethane in the troposphere is not expected to be an important fate process, because there is no chromophore for absorption of ultraviolet light (>290 nm) found in sunlight at tropospheric altitudes (Hubrich and Stuhl 1980; VanLaethem-Meuree et al. 1979). A laboratory experiment performed in sealed Pyrex ampules showed loss of 1,1,1-trichloroethane in

2 weeks under the influence of sunlight; however, catalysis by the Pyrex surface was probably responsible for the enhanced reactivity (Buchardt and Manscher 1978).

The relatively long tropospheric residence time for 1,1,1-trichloroethane suggests that migration to the stratosphere should be important. An estimated 11–15% of 1,1,1-trichloroethane released to the atmosphere is expected to survive and migrate to the stratosphere (Prinn et al. 1987; Singh et al. 1992). In the stratosphere, chlorine atoms produced from 1,1,1-trichloroethane by ultraviolet light may interact with ozone contributing to the destruction of the stratospheric ozone layer. Compared to CFC-11 (trichlorofluoromethane), the steady state ozone depletion potential of 1,1,1-trichloroethane has been estimated to be 0.1–0.16 (Gibbs et al. 1992; Solomon and Albritton 1992).

6.3.2.2 Water

Slow biodegradation of 1,1,1-trichloroethane can occur under both anaerobic and aerobic conditions. Anaerobic degradation of 1,1,1-trichloroethane is thought to occur predominantly through reductive dechlorination by methane-producing bacteria (Vargas and Ahlert 1987; Vogel and McCarty 1987) and by sulfate-reducing organisms (Cobb and Bouwer 1991; Klecka 1990). Determined experimental half-lives for anaerobic degradation using mixed culture bacteria ranged from 1 day to 16 weeks in the laboratory (Bouwer and McCarty 1983a, 1984; Hallen et al. 1986; Parsons et al. 1985; Vogel and McCarty 1987; Wood et al. 1985); based on a study from an injection well, after 3 months of injection, the predicted half-life of 1,1,1-trichloroethane in an aquifer was 200–300 days (Bouwer and McCarty 1984). Results obtained in a grab sample study of an aquifer suggest that anaerobic biodegradation of 1,1,1-trichloroethane will not occur (Wilson et al. 1983); however, the spiked concentration of 1,1,1-trichloroethane in the study, 1 mg/L, was in a range determined to be toxic to microorganisms (Barth and Bunch 1979; Benson and Hunter 1977; Vargas and Ahlert 1987). Another grab sample study, performed using more realistic concentrations, indicates that 1,1,1-trichloroethane slowly degrades under anaerobic conditions to 1,1-dichloroethane in groundwater (Parsons and Lage 1985; Parsons et al. 1985). However, when mixed anaerobic cultures were provided with acetate as primary substrate, the biodegradation of secondary substrate 1,1,1-trichloroethane occurred even without acclimation at concentrations exceeding 1 mg/L (Hughes and Parkin 1992). A laboratory study showed that anaerobic biodegradation of 1,1,1-trichloroethane did not occur under denitrification conditions even after 8 weeks of incubation (Bouwer and McCarty 1983b).

7 (Yao and Haag 1991). Therefore, reaction with ozone will not be an important process for the transformation of 1,1,1-trichloroethane present in natural bodies of water.

6.3.2.3 Sediment and Soil

Data are lacking on the degradation of 1,1,1-trichloroethane in soil. In a grab sample experiment, anaerobic degradation of 1,1,1-trichloroethane occurred slowly in soil (16% in 6 days) (Henson et al. 1988). If the microorganisms in the soil were first activated by using methane as a nutrient source, 46% of 1,1,1-trichloroethane degraded during the same period under aerobic conditions (Henson et al. 1988). Incubation of 1,1,1-trichloroethane in soil under aerobic conditions resulted in no measurable biodegradation (Klecka 1990).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

The manufacture and use of 1,1,1-trichloroethane was scheduled to be phased out by 2002 under the Clean Air Act (EPA 2004m). Since it is no longer in use, the levels estimated in the environment, other than near point sources, should drop to insignificant amounts. (unlikely, since it is still being produced!)

6.4.1 Air

1,1,1-Trichloroethane has been identified in urban, rural, and indoor air throughout the United States at concentrations shown in Table 6-3. Due to the nature of 1,1,1-trichloroethane's use, volatilization to the atmosphere is a predictable outcome, and thus, its widespread detection is not unexpected. It is the only chlorinated ethane regularly seen as a background pollutant in the troposphere (Spence and Hanst 1978). For the year 1980, an estimated global atmospheric quantity of 1,1,1-trichloroethane, based on absolute concentrations obtained over a 3-year period, was 2.58×10^9 kg (5,690 million pounds) (Prinn et al. 1983). An estimated average concentration of 0.14 ppb in 1980, based on a characterization of its sources, abundance, and atmospheric sinks, was also reported (Ramanathan et al. 1985). The data indicate that the average atmospheric concentration of 1,1,1-trichloroethane was 0.13 ppb for the middle of 1988 (Khalil and Rasmussen 1989). Based on absolute concentrations obtained over a 12-year period, a global atmospheric concentration of 157 ppt (0.157 ppb) was estimated for 1,1,1-trichloroethane in the middle of

1990 (Prinn et al. 1992). Atmospheric measurements at several surface stations made between 1978 and 1990 indicated that the global average concentration of 1,1,1-trichloroethane increased at a rate of 4.4±0.2% over this time period (Prinn et al. 1992).

wide variation

The measured concentration of 1,1,1-trichloroethane in urban air usually ranges from 0.1 to 1 ppb; however, levels ≤1,000 ppb have been observed in large urban areas or near hazardous waste sites. Representative monitoring data on the concentration of 1,1,1-trichloroethane in air can be found in Table 6-3. Rural levels of 1,1,1-trichloroethane are typically <0.2 ppb. The long atmospheric lifetime of 1,1,1-trichloroethane allows the compound to be carried a considerable distance from its initial point of release; detectable levels have been measured in numerous remote areas throughout the world and are shown in Table 6-3 (Class and Ballschmiter 1986; DeBortoli et al. 1986; Guicherit and Schulting 1985; Hov et al. 1984; Ohta et al. 1976; Rasmussen et al. 1982). The mean background concentration of 1,1,1-trichloroethane over subarctic North America in the summer of 1990 was 0.155 ppb (Wofsy et al. 1994). During a period of arctic haze, the concentration of 1,1,1-trichloroethane in the polluted Arctic air was 2–15% higher than in clean air over the Arctic (Khalil and Rasmussen 1993). The mean concentration of 1,1,1-trichloroethane in the troposphere over northwestern Pacific region (114–165 °E longitude) was found to range from 0.12 to 0.13 ppb (Blake et al. 1997, Table 6-3 Mohamed et al. 2002). The concentrations of 1,1,1-trichloroethane near industrial facilities emitting 1,1,1-trichloroethane were found to be only marginally higher than those measured at sites away from facilities emitting 1,1,1-trichloroethane.

The concentration of 1,1,1-trichloroethane in indoor air is variable, and seems to depend on individual practices, season, outdoor concentration, age of building, and building air-exchange characteristics (Cohen et al. 1989; Hartwell et al. 1987a, 1987b, 1992; Hisham and Grosjean 1991; Lioy et al. 1991; Wallace 1986; Wallace et al. 1986a, 1986b, 1988, 1989, 1991). For example, college students monitored simultaneously on the same campus were found to have levels of personal exposure varying by as much as two orders of magnitude (Wallace et al. 1982; Zweidinger et al. 1983). Further, two studies suggest that buildings with air conditioning may have higher levels of 1,1,1-trichloroethane in indoor air (Cohen et al. 1989; Hisham and Grosjean 1991). 1,1,1-Trichloroethane has been found at levels ≤70 ppb in newly constructed buildings (Wallace et al. 1987b). The concentration of 1,1,1-trichloroethane in new and recently renovated buildings was as high as 290 ppb (Rothweiler et al. 1992). New carpet and other new building materials that contain 1,1,1-trichloroethane may be responsible for higher levels in new and renovated buildings. During normal periods (no renovation or construction), the levels of total volatile

organics are inversely proportional to the air exchange rate of the building (Shields and Weschler 1992). Higher levels of 1,1,1-trichloroethane are expected to be found in indoor air during winter than any other season (Wallace et al. 1991). The effect of outdoor air on indoor air was demonstrated by the detection of higher levels of 1,1,1-trichloroethane during outdoor stagnation conditions when the levels were higher compared to levels under non-stagnation conditions (Lioy et al. 1991). Representative data taken from five geographic areas located throughout the United States report indoor concentrations of 0.3–4.4 ppb and outdoor concentrations of 0.11–0.92 ppb (Pellizzari et al. 1986). Several studies have determined the presence of 1,1,1-trichloroethane in products expected to be in most households (Section 6.5) (EPA 1987; Maklan et al. 1987; Sack et al. 1992; Spicer et al. 1987). An EPA Region V (Minnesota, Wisconsin, Michigan, Illinois, Indiana, and Ohio) National Human Exposure Assessment Survey (NHEXAS) detected a mean concentration of 1,1,1-trichloroethane to be 1.15 ppb in indoor air samples collected from residential areas from July 1995 to May 1997 (Bonanno et al. 2001). The maximum concentration of trichloroethane detected in the same study was 34 ppb.

6.4.2 Water

1,1,1-Trichloroethane has been identified in surface water, groundwater, drinking water, effluent, rain, snow, and urban runoff. The amount of the chemical detected in surface and groundwater depends upon the location of the sampling point. Concentrations in surface water removed from point-source emissions such as industrial waste water, hazardous waste sites, and spill locations are usually <1 ppb. In random samples of groundwater taken in the United States, concentrations have ranged from 0 to 18 ppb. Groundwater samples obtained near sources of release to soil or the ground have been as high as 11,000 ppb. Drinking water from surface or groundwater sources contained 1,1,1-trichloroethane concentrations of 0.01–3.5 ppb.

Data on the occurrence of 1,1,1-trichloroethane in water are presented in Table 6-2. Data on the concentration of 1,1,1-trichloroethane in effluent can be found in Table 6-4.

1,1,1-Trichloroethane was found in groundwater at hazardous waste sites in 18.9% of 178 sites from the Comprehensive Emergency Response, Compensation and Liability Act (CERCLA) database, making it the seventh most frequently detected compound in this study (Plumb 1987). It was found in water

samples from 42 of 357 Contract Laboratory Program (CLP) sites; the concentration range of the mean values was 1.75–1,100 ppb (Viar 1987).

6.4.3 Sediment and Soil

Monitoring data on the occurrence of 1,1,1-trichloroethane in soil are not as extensive as for water or air, which precludes an estimate of typical levels found in soil. The reported levels of 1,1,1-trichloroethane in soils are shown in Table 6-5. In two grab soil samples taken in 1980 from two former sludge lagoons of a solvent recovery operation at Southington, Connecticut, the measured concentrations of 1,1,1-trichloroethane were 23,000 and 120,000 ppb (Hall 1984). The limited data on the concentration of 1,1,1-trichloroethane in soil may be due to its rapid volatilization from soil, its ability to leach through soil, or both. The concentrations of 1,1,1-trichloroethane in sediments are shown in Table 6-2. The mean concentration of 1,1,1-trichloroethane in sediments from a river passing through an industrial area in Japan was 0.4 ppb, although it was not detected in the river water or in the sediment of a river passing through a non-industrial area (Grotoh et al. 1992).

6.4.4 Other Environmental Media

Limited data on the occurrence of 1,1,1-trichloroethane in other media were located. 1,1,1-Trichloroethane has been found in raw, processed, and prepared food products. These data are presented in Table 6-6. 1,1,1-Trichloroethane has been found in fish and shrimp taken from the Pacific Ocean at average concentrations of 2.7 and <0.3 ppm, respectively (Young et al. 1983). It has also been detected in clams and oysters from Lake Pontchartrain, Louisiana, with mean concentrations ranging from 39 to 310 ppm (Ferrario et al. 1985) and from a polluted river in Japan at concentrations ranging from 0.6 to 1.8 ppb wet weight (wt/wt) (Grotoh et al. 1992). 1,1,1-Trichloroethane was detected in 2 of 265 table-ready foods of FDA Total Diet Study at an average concentration of 12.7 ppb (Heikes et al. 1995).

1,1,1-Trichloroethane has been detected in four shoe and leather glues in Denmark in the concentration range 0.1–2.7% (wt/wt) (Rastogi 1992). Six samples of glues manufactured in the United States and in Europe and used for assembling various consumer goods and toys contained 1,1,1-trichloroethane in the concentration range 0.002–97.5% (wt/wt) (Rastogi 1993). In various brands of imported typing

correction fluids in Singapore, the equilibrium vapor phase concentration of 1,1,1-trichloroethane ranged from <1 to 95% (v/v) (Ong et al. 1993).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The manufacture and use of 1,1,1-trichloroethane was scheduled to be phased out by 2002 under the Clean Air Act (EPA 2004m). Since it is no longer in use, the exposure of the general population should drop to insignificant levels.

The ubiquitous occurrence, in the past, of low levels of 1,1,1-trichloroethane in ambient air and other environmental samples, together with the fact that many consumer products used to contain this chemical, suggests that much of the general population of the United States was exposed to low levels of 1,1,1-trichloroethane. This exposure could have occurred occupationally, environmentally, or as a result of the use of commercial products that contain 1,1,1-trichloroethane. 1,1,1-Trichloroethane has been detected in the blood, milk, breath, and urine of humans. An EPA Region V (Minnesota, Wisconsin, Michigan, Illinois, Indiana, and Ohio) National Human Exposure Assessment Survey (NHEXAS) detected a mean concentration of 1,1,1-trichloroethane to be 0.05 ppb in blood samples collected from July 1995 to May 1997 (Bonanno et al. 2001). The maximum concentration of trichloroethane detected in the same study was 2.7 ppb. Data on human body burdens associated with this compound can be found in Table 6-7. Table 5-2 provides a sampling of consumer products containing 1,1,1-trichloroethane. The levels of this chemical in human breath have been correlated with its levels in personal air by probability-based population studies (Wallace et al. 1985, 1986c, 1987a, 1988).

If the average urban concentration of 1,1,1-trichloroethane is taken to be 1 ppb and the average rural concentration is taken to be 0.1 ppb, then daily non-occupational intakes of 108 and 10.8 μg/day, respectively, can be obtained based on an average human air intake of 20 m^3/day. In areas where 1,000 ppb have been measured, the daily intake using this methodology would be 108 mg. However, Wallace et al. (1984a) have determined that the mean daily air exposure for 12 subjects from urban New Jersey and Research Triangle Park, North Carolina, was 370 mg. Further, the mean daily intake from all sources (air, food, and water) was between 50 and 1,000 mg/day for 1,1,1-trichloroethane (Wallace et al. 1984a).

1,1,1-Trichloroethane has been detected in newly constructed buildings (Wallace et al. 1987b). In a recent "shopping basket" survey, 1,1,1-trichloroethane was found in 216 of 1,159 common household products preselected to contain solvents at concentrations >0.1% by weight (Sack et al. 1992). In a similar study, 1,1,1-trichloroethane was found in all 67 categories of household products (1,026 brands tested) likely to be in the average U.S. home (EPA 1987; Maklan et al. 1987). The categories of these common household products are given in Table 5-2. The occurrence of 1,1,1-trichloroethane in 62% of the effluent samples taken from a community septic tank also suggests the presence of this compound in household products (De Walle et al. 1985).

Human exposure could occur directly via ingestion of contaminated water, but also indirectly through the inhalation of 1,1,1-trichloroethane that has volatilized from contaminated tap water. Based on a theoretical concentration of 1 mg/L (ppm) of 1,1,1-trichloroethane in tap water, the average estimated air concentrations for the entire house, bathroom, and shower stall were 2.3×10^{-4}, 5.1×10^{-3}, and 2.6×10^{-2} mg/L, respectively (McKone 1987). For a tap water concentration of 20 mg/L, the estimated daily exposure to 1,1,1-trichloroethane was 20.0 mg from ingestion and 22.8 mg from inhalation while showering (Foster and Chrostowski 1986). The Total Exposure Assessment Methodology (TEAM) studies demonstrated that levels of personal air exposure determined using samples obtained on the same day could vary by orders of magnitude for subjects living in the same municipality, most likely as a result of variances in consumer practices and occupation (Hartwell et al. 1987a, 1987b, 1992; Wallace 1986, 1987; Wallace et al. 1986a, 1986b, 1988, 1989; Zweidinger et al. 1983). The maximum exposure levels of 1,1,1-trichloroethane during personal activities were: 185 ppb when visiting the dry cleaners, 18.5 ppb when working in a chemistry lab, 12 ppb when working as a lab technician, 48 ppb when using household cleaners, 20 ppb when using pesticides, and 20 ppb when using paint (Wallace et al. 1989). Exposure of the general population from the use of commercial products may be more significant than exposure resulting from industrial release.

According to the National Occupational Exposure Survey (NOES) conducted by NIOSH between 1981 and 1983, it has been statistically estimated that ≈2,528,300 workers in the United States were potentially exposed to 1,1,1-trichloroethane (NIOSH 1990). The largest number of workers are exposed in the following types of industries/services: sewing machine operators in apparel industry; registered nurses, maids, janitors and cleaners in hospitals; electricians, technicians, assemblers, installers, machinists and repairers in electrical and electronic industry; and janitors and cleaners in building maintenance service. From the existing monitoring data, it appears that most occupational exposure occurs by inhalation.

There are no existing studies that have monitored the level of exposure from 1,1,1-trichloroethane to children. Most uses of 1,1,1-trichloroethane are associated with occupational purposes, so it is unlikely that children will receive significant doses. Under extreme conditions where products containing high concentrations of 1,1,1-trichloroethane are used in the presence of children in an enclosed area with little or no ventilation, children could receive significant exposure. There are studies that examine the exposure to children from parents' work clothes, skin, hair, tools, or other objects removed from the workplace (NIOSH 1995); however, this type of "take home" or secondary exposure is unlikely due to the high volatility of methylene chloride. Additional exposure from consumer products can occur, but is unlikely to be significant, although little data are available at this time.

It is not known whether children differ in their weight-adjusted intake of 1,1,1-trichloroethane. However, children drink more fluids per kg of body weight than adults (NRC1993) and 1,1,1-trichloroethane has been detected in drinking water (Section 6.4.2, Table 6-2).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The general population is potentially exposed to low levels of 1,1,1-trichloroethane through the ingestion of contaminated water or food. The manufacture and use of 1,1,1-trichloroethane was scheduled to be phased out by 2002 under the Clean Air Act (EPA 2004m). Since it is no longer in use, the exposure of the general population should drop to insignificant levels. Low levels of contamination in drinking water sources have been documented (Althoff et al. 1981; Barkley et al. 1980; Burmaster 1982; EPA 1986a; Krill and Sonzogni 1986; Wallace et al. 1984a; Zaki 1986). According to Table 6-2, levels of 0.01–12,220 ppb 1,1,1-trichloroethane have been found in drinking water sources. 1,1,1-Trichloroethane is used as a component of adhesives for food packaging, and this practice may contribute to human exposure by ingestion (Miller and Uhler 1988). Airtight, highly-insulated houses are likely to have high indoor concentrations from use of household products containing 1,1,1-trichloroethane. Very high levels of exposure are expected to occur for those who intentionally inhale 1,1,1-trichloroethane for its euphoric/narcotic properties.

Workers involved in processes using this compound may encounter high exposure levels. Occupations in which 1,1,1-trichloroethane has been found in the air are given in Table 6-8. Analysis of these data

shows that ambient air concentrations in industries using 1,1,1-trichloroethane are up to 4 orders of magnitude higher than what is typically found in urban air.

1,1,1-Trichloroethane was used in some adhesive remover pads of incubators in intensive care nurseries, and there is evidence that infants in incubators could be exposed to high concentrations of 1,1,1-trichloroethane (Gallagher and Kurt 1990).

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1,1-trichloroethane is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,1,1-trichloroethane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of 1,1,1-trichloroethane are well documented, and little additional information in this area is required. Only one BCF for 1,1,1-trichloroethane was located in the available literature. This value is, however, consistent with what would be expected based on the other physical and chemical properties of 1,1,1-trichloroethane.

Production, Import/Export, Use, Release, and Disposal. Data on the production, use, release, and disposal of 1,1,1-trichloroethane in the United States are well represented in the literature. The

Bioavailability from Environmental Media. Numerous toxicokinetic and toxicity studies in humans and animals have demonstrated the bioavailability of 1,1,1-trichloroethane from air and drinking water. Although some data on the bioavailability of 1,1,1-trichloroethane from air to mammalian skin (Mattie et al. 1994), and from air to other mammalian tissues (blood, muscle, liver) (Connell et al. 1993) are available, no studies on the bioavailability of 1,1,1-trichloroethane from food or soil were located. Some of the important routes of exposure to 1,1,1-trichloroethane for residents near waste sites will be inhalation of airborne dusts, ingestion of soil (children) and dermal contact with contaminated soil (mostly children). Therefore, it would be helpful to develop reliable data for the bioavailability of 1,1,1-trichloroethane from dust as a result of inhalation of contaminated airborne dust, from soil as a result of ingestion of soil, and from soil as a result of dermal contact with soil. probably so

Food Chain Bioaccumulation. 1,1,1-Trichloroethane is not believed to bioconcentrate in fish and aquatic organisms; thus, it is not expected to biomagnify in the food chain. There are limited data regarding food chain biomagnification of 1,1,1-trichloroethane.

Exposure Levels in Environmental Media. Volumes of data exist on levels of 1,1,1-trichloroethane in environmental media, with the exception of levels in soil samples. Continued monitoring of environmental media is warranted. Blind monitoring at this stage, however, might be replaced with methods that allow both the continued determination of the environmental burden of 1,1,1-trichloroethane and correlation with human burden, like that performed in the TEAM studies. These and other studies have estimated human intake of 1,1,1-trichloroethane from environmental media. For members of the general population near hazardous waste sites, total exposure to 1,1,1-trichloroethane will include exposure from environmental media and exposure from consumer products.

Reliable monitoring data for the levels of 1,1,1-trichloroethane in contaminated media at hazardous waste sites are needed so that the information obtained on levels of 1,1,1-trichloroethane in the environment can be used in combination with the body tissue/fluid levels of 1,1,1-trichloroethane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. yes!

Exposure Levels in Humans. 1,1,1-Trichloroethane has been detected in human tissues and expired air. Studies have recently determined that the potential for exposure of the general population may be significantly higher inside the home. Additional information that correlates the lifestyle of the

individual with the total body burden of 1,1,1-trichloroethane would aid in reducing future exposure to the general population. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. A study on usefulness of intervention methods in cases of inhalant abuse by pregnant women would be helpful. More research is needed to rule out concomitant risk factors and to identify specific chemicals and patterns of use associated with adverse effects.

Children are at a greater risk of inhalation exposure to 1,1,1-trichloroethane as they breathe in more air per kilogram of body weight than an adult. They also spend more time closer to ground because of their height. 1,1,1-Trichloroethane vapors, being heavier than air, tend to concentrate closer to the ground, thereby increasing the risk for children. No data are available on the exposure of the children to 1,1,1-trichloroethane present in the air.

Means of protecting young children from ingestion of home products containing 1,1,1-trichloroethane need study and action. Child-proof containers and clearer warnings to parents should be considered to avoid unwanted exposure.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for 1,1,1-trichloroethane were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2004) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring 1,1,1-trichloroethane, its metabolites, and other biomarkers of exposure and effect to 1,1,1-trichloroethane. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

In the analysis of 1,1,1-trichloroethane in biological materials, a key factor in the determination is the sample matrix under consideration. In the broadest sense, this can be broken down into liquid samples (e.g., blood or urine), solid samples (which would include adipose tissue, liver samples), and expired air samples. After 1,1,1-trichloroethane has been liberated from the sample matrix, a number of similar techniques can then be used to complete the analysis. A synopsis of these methods can be found in Table 7-1. In general, the methods for determining the metabolites of 1,1,1-trichloroethane are the same as those used for the parent compound, with slight modifications (Nolan et al. 1984).

The quantification of 1,1,1-trichloroethane in blood and urine samples can be achieved by the initial use of purge and trap methodology (Antoine et al. 1986; Barkley et al. 1980). This technique involves the liberation of the volatile chlorinated hydrocarbon by bubbling an inert gas through the sample matrices at elevated temperatures (≈50–95 °C). Higher temperature increases the vapor pressure of the compound, and the bubbling action serves, essentially, to increase the gas-liquid partition, and thus volatilize the compound of interest. The gaseous sample is collected on an adsorption tube, which frequently uses a polymeric sorbent such as Tenax GC.

At this point, the sample is analyzed by gas chromatography (GC), the analytical method of choice for volatile halogenated hydrocarbons. Information on the analysis of these samples by GC is presented in Section 7.2, with a discussion of the advantages and disadvantages of each method. The technique of Antoine et al. (1986) showed a 5% variance on a series of 2 ppb spiked samples, and the analysis had a linear response ranging from 0.5 to 50 ppb. Although infra-red spectrometry has less sensitivity than electron capture detectors (ECD), Hall electroconductivity detectors (HECD), and mass spectrometric detectors (MS), it has been used to quantify the levels of 1,1,1-trichloroethane in biological samples (IARC 1979).

The concentration of 1,1,1-trichloroethane in solid samples can be determined by headspace techniques, which involve analysis of the air above a heated sample in either a dynamic or a static system. In a static system, an aliquot of the atmosphere above the sample is obtained and analyzed by direct GC. In a dynamic system, an inert gas is passed over the top of a heated, rapidly stirred suspension of sample in water (Stanley 1986a, 1986b). The gas stream is then passed through an adsorption tube, trapping the volatile compounds. For adipose tissue, the detection limits were 0.01 mg/kg and the average recovery for spiked samples (concentration range 0.15–0.44 μg/20 g tissue) was 105%, with a precision of 11.8% (Stanley 1986a, 1986b).

in a dessicator?

In biological samples, losses during the sample preparation stage (weighing, transferring, etc.) can arise due to the volatility of 1,1,1-trichloroethane or from an incomplete recovery from the biological matrix. Samples should be analyzed shortly after they are obtained. Otherwise, they should be carefully stored at low temperature, preferably in a freezer. Handling and manipulation also should be kept to a minimum, preventing both premature loss by volatilization and contamination of the sample through the adsorption of vapors from ambient air. The need for blank water with very low levels of volatile organic compounds (VOCs) has increased because of the constant improvement in the sensitivity of detection of these VOCs. A method that uses distillation in conjunction with helium stripping has been described to obtain high purity blank water (Cardinali et al. 1994).

7.2 ENVIRONMENTAL SAMPLES

A short description of the methods used for analysis of 1,1,1-trichloroethane in environmental samples is presented in Table 7-2. An extensive list of methods for analysis of 1,1,1-trichloroethane in

environmental samples can be compiled from the literature. Two methods are commonly used for collection of 1,1,1-trichloroethane and other volatile organics in ambient and occupational air. One method uses adsorbents to trap and concentrate organics in air, and the other method uses passive stainless steel canisters (SUMMA canisters). The advantage of SUMMA canisters is that sample breakthrough does not occur with this method as it may occur with adsorbent tubes (Hsu et al. 1991). The disadvantages of the canister method are its inability to concentrate pollutants during sample collection and the potential analytical problems associated with the presence of moisture in the sample (Bianchi and Varney 1993). In all methods, however, there is a consensus that after the sample collection and preparation stage, mixture separation and quantitative analysis is best done with GC, coupled with an assortment of detectors. Standardized methods, with slight alterations, also can be used for determining the metabolites of 1,1,1-trichloroethane (Hallen et al. 1986; Parsons et al. 1985; Vogel and McCarty 1987).

The analysis of 1,1,1-trichloroethane in occupational air samples can be accomplished by NIOSH method 1003 (NIOSH 1987). The sample is obtained in the field with a pumping system to pass a measurable quantity of air (≈3 L) through a tube loaded with a solid sorbent, such as charcoal. Extraction of the tube with the solvent CS_2 liberates the 1,1,1-trichloroethane collected, an internal standard is added, and quantitation is then achieved by GC. For packed column analysis, an OV-101 column using a flame ionization detector (FID) is given as the preferred choice (alternates, including capillary columns, are acceptable). For the estimation of low levels of 1,1,1-trichloroethane in ambient air, thermal desorption following collection of the sample in an absorbent trap is the method of choice (Frank and Frank 1988).

Capillary columns are used to separate 1,1,1-trichloroethane from the other components in a mixture. Capillary columns provide wider versatility offering superior resolution of components. A comparison of capillary and packed column for analysis of volatile organics by GC is available (Clark and Zalikowski 1990). Narrow-bore capillary columns have high resolving power, but may not be suitable for headspace analysis because of easy column saturation (Ohno and Aoyama 1991). Wide-bore capillary columns are suitable in such cases (Ohno and Aoyama 1991). Different detectors can be used; ECD, HECD, and MS have been described. The MS is the most selective detector, but the HECD is the most sensitive. Both closed path and open path Fourier transform infrared spectrometry (FTIR) have recently been used for the determination of 1,1,1-trichloroethane in air (Carter et al. 1992; Trocha and Samimi 1993; Xiao and Levine 1993). Although the FTIR methods have higher detection limits than the some of the other

conventional methods, they afford the opportunity of remote monitoring of real-time samples (Xiao and Levine 1993).

In the analysis of 1,1,1-trichloroethane in air, the weakest link in analysis is irreversible adsorption of the desired compound to the sorbent material during sample collection. For highly volatile, nonpolar compounds such as 1,1,1-trichloroethane, complete removal of the substrate may not occur if the adsorbent irreversibly adsorbs the substrate.

The collection methods commonly used for water and aqueous effluents are grab or proportional sampling. However, a solid phase microextraction method, which involves exposing a fused silica fiber coated with a stationary phase to the aqueous sample until equilibrium is achieved, has been proposed as a collection method (Arthur et al. 1992). Analysis for 1,1,1-trichloroethane in municipal and industrial waste water is described in EPA method 601—purgeable halocarbons (EPA 1982a). A 5 mL grab sample is connected to an apparatus called a purging chamber. This chamber allows for an inert gas to be sparged through the water sample, carrying the 1,1,1-trichloroethane onto an adsorbent tube. The organics are subsequently desorbed from the adsorbent tube by rapid heating and back flushing into the GC column. Analysis is then made by GC elution using an HECD. Detection limits for this method are given as 0.03 μg/L, with a 75% average recovery for spiked samples. EPA test method 624, purgeables, also can be used for the analysis of 1,1,1-trichloroethane in waste water (EPA 1982a). This method is similar to method 601, except that MS is used for quantitation.

EPA method 502.1 can be used in the analysis of 1,1,1-trichloroethane in finished or raw source water (EPA 1986a). This method is analogous to method 601. The detection limit for this method is 0.003 μg/L, with an average recovery of 93%.

The EPA guidelines for contract laboratories (EPA 1986c) include methodology for the analysis of groundwater and soil samples. The method for water analysis is similar to method 524.1. Detection limits for this method are given at 5 μg/kg.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1,1-trichloroethane is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,1,1-trichloroethane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. The urinary concentration of 1,1,1-trichloroethane can be used as an appropriate biological indicator of exposure (Imbriani et al. 1988; Salkinoja-Salonen and Jokela 1991). Both in the experimentally exposed subjects and in the occupationally exposed workers, the urinary concentration of 1,1,1-trichloroethane showed a linear relationship to the corresponding environmental time-weighted average concentration with a correlation coefficient of 0.90–0.95 (Imbriani et al. 1988). Analytical methods of sufficient sensitivity are available to determine 1,1,1-trichloroethane in urine (Imbriani et al. 1988; Salkinoja-Salonen and Jokela 1991).

Effect. There is no known effect of 1,1,1-trichloroethane that can be quantitatively related to its exposure.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.