1,1-dichloroethane

Reviewer #1

Overall the Toxicological Profile for 1, 1-dichloroetahne is well written and proper details are provided. However, a few suggestions to improve it further are given below:

1. Page 27, line 16 - Type and should be' 1, 1-dichloroethane'. Additional 'period' should be removed.

2. Page 81, line 2 - should be written as (M-CH_3) or more correctly as (M: -CH_3).

3. Page 49 -Table 4-1. Grayson 1978 could not be found under references and thus all synonym(s) could not be checked but '1, 1-dichloro-(9Cl)' appears to be incomplete or wrong. Similarly, 'ethane' does not make sense. Although 'chlorinated hydrochloric ether' is mentioned in Weiss 1986, it does not make sense as 1, 1-dichloroethane cannot be called as ether.

1,1 Dichloroethane

Toxicological Profile

Reviewer #2

General comments

As indicated in this Toxicological Profile, the chlorinated chemical 1,1-dichloroethane is basically an intermediate product in the manufacture of other chlorinated solvents and monomers (p. 53). The compound became one of public interest because it was found in a number of hazardous waste sites in the United States (p. 54). It is also an intermediate in the microbial dehalogenation of the solvent 1,1,1-trichloroethane (p.62) and therefore a potential drinking water pollutant.

As far as can be seen from the limited toxicological data available, 1,1-dichloroethane appears to be of low toxicity, relative to other chlorinated ethanes/methanes. The low toxicity and the fact that 1,1-dichloroethane is no finished end product, are the likely reasons for the limited toxicological data base. As a result of this lack of relevant toxicity data, by which the relevant target systems within the organism are identified and the lack of associated dose/concentration-response relationships, inhalation and oral MRLs for 1,1-dichloroethane are not derived.

Specific issues

Chapters 1 and 2

There are no specific comments.

Chapter 3 Health Effects

As far as repetitive dosage is concerned, the major sources of information are the oral NCI bioassay (Weisburger, EHP 21: 7-16, 1977), the oral studies of Klaunig et al. 1986) and the inhalation studies of Hofmann et al. (1971). A relevant point in the oral studies (administration in corn oil or in drinking water) is the high volatility of the test compound, with a boiling point of 57.3°C (p.50). The relatively old publications say little about how evaporation of the test compound from the test solution was prevented, and how the test solutions applied were analytically controlled. This appears to be most relevant in the drinking water study. This factor could well account for differences in the study outcomes.

Genotoxicity (p.22 ff)

There are positive and negative study results (Table 3-3). As far as Ames-test data are concerned, the positive studies were performed in a closed system ("desiccator assay"). Such closed-system studies clearly provide more relevant information concerning mutagenic properties of gaseous or volatile compounds than common "treat-and-plate" or pre-incubation assays (Castelain et al., Mutagenesis 8(5): 387-393). A minor metabolite being mentioned in this document (Table 3-4, p. 29), which has mutagenic and DNAreactive properties, is chloroacetaldehyde. This could eventually explain the metabolism-mediated DNA reactivity that is discussed on p. 24

An editorial point: p.24, l. 16: Glutathione-S-transferase (not Glutathione-s-transferase).

Metabolism (p.27ff)

The data in the chapter on effects of induction/inhibition (p.27, l. 21-31) very much suggest that not just cytochrome P-450, but specifically CYP2E1 is relevant for the oxidative metabolism. This would be in concordance with what is known on structurally related chlorinated alkanes.

Figure 3-3: There is a major mistake in this figure, as the formula of acetyl chloride is wrong; 1 C-atom is missing! Correct would be: CH_3-COCl

Editorial points: p. 27, l.16: 1,1-dichloroethane. (not: 1,1 dichloro-ethane..)
p.27, l.21: "Induced/uninduced microsomes" is lab slang! Not the microsomes are induced, but microsomal enzymes or cytochrome(s) P-450.

PBPK Models (chapter 3.4.5, p. 31)

I understand that the text printed in bold is important because of administrative reasons. Nevertheless, going through the very detailed pages of 31/32, plus the accompanying complicated figure 3-4 (p.33), just to see then that no PBPK models were identified, makes very odd reading for a toxicologist!
As a compromise: Could the figure 3-4 be deleted in this case?

Chapter 3.8.2 (p.38, l. 20)
This sentence reads curious: The early (what is early?) part of the 20th or 21st century??

Identification of Data Needs (3.12.2)

p.44, lines 2/3: I would not directly compare 1,1-dichloroethane with 1,2-dichloroethane. The latter is genotoxic because of the formation of a specific thiiranium (episulfonium) ion, which cannot be formed from 1,1,-dichloroethane. I therefore propose to delete: …1,2-dichloroethane and certain…

Figure 6-1 (p.55)
A legend is missing from my print: What do the different fillings in the map of the US federal states mean?

There are no other specific comments regarding chapters 4 ff.

There are also no comments to Appendix A, as no MRLs are derived.

Summary
I agree with the document, its derivations and conclusions.
I feel that the document has been generally well compiled and edited.
There are some remarks concerning further explanations and/or changes, as specified above.

Comments on Toxicological

Profile for 1,1-Dichloroethane

Reviewer #3

CHAPTER 1. PUBLIC HEALTH STATEMENT

This chapter is well written and should be easily understood by the public. The tone of the chapter is factual rather than judgmental.

Some of the major headings are stated as a question and some are not. The answers should address any concerns of the lay public. The summary statements are well supported by the technical discussion in the remaining part of the chapter and by the tabular data.

I don't think any of the scientific terms are too technical. Some of the lay public may not understand the word "volatilize", but this is unlikely.

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

There is relatively little information regarding human health effects related to exposure to 1,1-dichloroethane (1,2-DCE). I could not find additional information in the literature on human health effects. The development of cardiac arrhythmia's in humans exposed to 1,1-DCE as an anesthetic is the only known effect of this compound in humans and the dose levels required to elicit this effect were very high- much higher than one would expect from sources in the environment.

The renal toxicity observed in cats exposed by inhalation to 1,1-DCE is not likely to be of concern to humans because of the high levels of exposure (500 – 1000 ppm), and the lack of nephrotoxicity in other animal species except in mice given a lethal dose. The compound did not produce hepatotoxic effects in several animal species. In the single developmental toxicity study, the compound retarded fetal development at 6,000 ppm, again a very high dose. The carcinogenicity data are inconclusive – the NCI study data are compromised by the high

mortality rates of the animals. The study of Klaunig, et al., appears to be well conducted and it indicated that 1,1-DCE is neither an initiator or promoter of carcinogenesis. In summary, the current animal data suggest that 1,1-DCE may not represent a toxic or carcinogenic hazard to humans.

With one exception, the exposure conditions have been adequately described. On page 32, the document should clearly indicate that the route of exposure used in the study of Hoffman, et al.,1971 was by inhalation.

CHAPTER 3. HEALTH EFFECTS

Section 3.1 INTRODUCTION. OK as is.

Section 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE.

Toxicity – Quality of Human Studies

The only study reporting toxic effects of 1,1-DCE in humans is that of the development of cardiac arrhythmias at anesthetic doses. There are no other data in humans exposed to this compound. The document should state in more detail how many humans were exposed to 1,1-DCE as an anesthetic and the percentage of those exposed who developed arrhythmias. If known, age, gender and preexisting conditions that might have made some humans more likely to develop arrhythmias than others should also be presented.

Due to the lack of appropriate data, no NOAELs or LOAELs for 1,1-DCE were developed for humans. No statistical tests were used.

I am not aware of other studies that might be important for evaluating the toxic effects of 1,1-DCE in humans.

Toxicity – Quality of Animal Studies

The animal toxicity studies for 1,1-DCE are limited. With regard to the studies reported, the document lacks information on the number of animals, animal care, and sufficient number and magnitude of dose levels used in the studies. One obvious concern is that, in view of the human data, a study to evaluate the effects of 1,1-DCE on the cardiovascular system of animals is clearly warranted.

The nephrotoxicity results in cats in the Hoffman et al. study are difficult to interpret because the specific species of cat is not given (maybe the different species vary in susceptibility to the renal toxic effects of chemicals?) and 1,1-DCE did not produce similar renal effects in rats, rabbits or guinea pigs. It's not clear whether humans would respond to 1,1-DCE like cats or other animal species. The animal species used to evaluate the hepatotoxic effects of 1,1-DCE given by different routes are appropriate.

The conclusions drawn by the authors of the document for all of the reported studies are appropriate. However, the appropriateness of the statistical tests could only be determined by examining the original studies since the tests used in the studies are not described in the document. The major studies by Hoffman,et al, the NCI and Klaunig, et al. used the appropriate statistical tests.

The NOAELS and LOAELS identified for 1,1-DCE for each study are appropriate. A major concern, however, is that all of the toxicity studies reported effects on a limited number of target organs. No one study evaluated the effects of 1,1-DCE on multiple organ sites in the same animal species when administered at several dose levels.

I am not aware of other studies that may be of importance in evaluating the toxicity of 1,1-DCE.

There is one change that should be made in the document. On page 44, the statements under the headings, "Reproductive Effects" and "Developmental Effects" should be switched.

Levels of Significant Exposure (LSE) Tables and Figures

The LSE Tables are complete and self explanatory. The Figures however, reference a number of animal species in the footnotes for which there is no data; e.g., ferret, pigeon, gerbil, etc. These should be eliminated. In addition, the actual exposure levels in the figures should be referenced rather than try to estimate the levels from their proximity to 1000 ppm or 10,000 ppm, etc. The “Users Guide” clearly explains how to use the LSE tables and figures.

I think the catagories of “serious” and “less serious” for the LOAELs are OK as presented because they reflect the data from the studies performed. However, in my view, the overall database on the toxicity of 1,1-DCE is limited so these catagories could change as more data are developed.

Minimal Risk Levels for 1,1-DCE have not been developed and this is justified based upon the limited available data.

Evaluation of Text

The major limitations of the studies have been adequately and accurately discussed. I see no need to change the discussions as is.

The endpoints have been critically evaluated for their relevance to both animals and humans.

Bottom line statements have been made for all of the most important endpoints in the animal studies with regard to their relevance for humans.

The conclusions regarding the toxicity and carcinogenicity of 1,1-DCE are appropriate given the overall database.

Adequate attention has been given to dose-response relationships however, there is limited information in this regard.

There is no animal data regarding the effects 1,1-DCE on the cardiovascular system as was noted in humans exposed to the compound as an anesthetic.

Section 3.3 GENOTOXICITY.

The genotoxicity data on 1,1-DCE is not conclusive. The results from one lab to another vary. It does not appear to be a strong genotoxin.

Section 3.4 TOXICOKINETICS.

There is no data on the absorption of 1,1-DCE per se in humans or in animals when given by inhalation, although the comments regarding the absorption of similar isomers; e.g., 1,2-DCE, in animals by this route are likely to be reflective of 1,1-DCE. Similarly, no data is available regarding dermal or oral absorption in humans or animals. Thus, there is a lack of absorption data on the likely routes of human exposure (inhalation, dermal, oral). Similarly, with the exception of a study in which 1,1-DCE was given i.p., there is no data on the tissue distribution of 1,1-DCE. The i.p. data is irrelevant as an exposure route to humans. No PBPK models exist for 1,1-DCE.

The metabolic scheme for 1,1-DCE given in Figure 3-3 is reasonable based upon the available data, however, the scheme has not been fully confirmed. More studies are necessary to fully characterize the pharmacokinetics of 1,1-DCE in humans and animals.

Section 3.5 MECHANISMS OF ACTION

Very little is known about the mechanism(s) of action of 1,1 -DCE. The possibility that it might act as an endocrine disruptor is largely speculative. Potential effects on cellular macromolecules such as DNA have not been investigated, particularly when administered by the most likely routes of human exposure.

Section 3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS.

As mentioned above, the possibility that 1,1-DCE could act as an endocrine disruptor are largely speculative.

Section 3.7 CHILDREN'S SUSCEPTIBILITY

The discussion on the effect of toxic agents in children versus adults is accurate. One might expect children to be more susceptible to the toxic effects of 1,1-DCWE than adults. The one study by Schwetz et al., 1974, demonstrated developmental effects of 1,1-DCE in rats; i.e., an increase in the incidence of delayed ossifications in the fetuses of dams exposed to 6,000 ppm of the compound on gestation days 6-15. Presumably, this exposure occurred by inhalation. It is difficult to extrapolate this data to humans because the exposure level is very high.

Section 3.8 BIOMARKERS OF EXPOSURE AND EFFECT

The discussion of biomarkers of exposure, effect and susceptibility is standard for any chemical. There are no established biomarkers of susceptibility, exposure or effect for 1,1-DCE in humans. Serum biomarkers could not be identified in the National Health and Nutrition Survey or in the blood of patients treated with 1,1-DCE as an anesthetic.

Section 3.9 INTERACTIONS WITH OTHER CHEMICALS

There are no data on the actual interaction of 1,1-DCE with other chemicals. However, because 1,1-DCE is detoxified by glutathione, it is reasonable to assume that glutathione depletion by other chemicals could increase the toxicity of 1,1-DCE. Similarly, compounds that influence the expression of P450's involved in the metabolic activation of 1,1-DCE may also effect its toxicity. This could be the reason that ethanol increases the metabolism of 1,1-DCE.

There was no discussion of potential interaction of 1,1-DCE with other chemicals that might occur at wastesites.

Section 3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No populations that are unusually susceptible to the toxic and carcinogenic effects of 1,1-DCE have been identified. The discussion generally describes some of the reasons why some individuals could be more susceptible to 1,1-DCE than others. Although largely speculative, I agree with the NIOSH (1978) classification of four groups that could be more susceptible to the compound due to high exposures. Similarly, children and the elderly might be more susceptible due to metabolic considerations and individuals with varying levels of enzymes that detoxify and activate the compound could well differ in susceptibility. I am not aware of additional studies in this area.

Section 3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section is very brief and provides little information as to what steps might be taken to reduce the toxic effects of 1,1-DCE or to influence its absorption, metabolism and tissue distribution. Perhaps the document could be more speculative in this respect rather than simply point out the lack of data.

Section 3.12 ADEQUACY OF THE DATABASE

This section summarizes the existing database on the toxicity of 1,1-DCE and identifies a significant number of “data needs”. I think the data needs are presented in a neutral, non-judgmental fashion. They are very broad however, and would require prioritization. In my view, the data need of highest priority is to evaluate the possibility of conducting epidemiologic and human dosimetry studies in persons exposed to 1,1-DCE in industrial settings. These would be retrospective studies to determine if prior chronic exposure to the compound may have led to toxic/carcinogenic effects. The document states that this would not be a fruitful approach because of potential problems in distinguishing 1.1-DCE effects from those of similar compounds in the workplace. While this might be the case, if no toxic effects could be identified in humans known to be exposed for long periods to 1,1-DCE and potentially other similar compounds in the workplace setting, then is it worth embarking on an ambitious series of experimental studies to evaluate the toxicity of the compound particularly in a period of limited budgets?

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

The information presented in this chapter is largely in two tables. I am not aware that any of the values are incorrect or missing. The information is presented on only one form of the chemical which is appropriate.

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

This chapter does an acceptable job of describing the overall production and use of 1,1-DCE on a state-by-state basis in the U.S. It appears likely that one could identify high production areas from which to conduct epidemiologic/dosimetry studies to identify potential toxic effects in humans. The methods of production and disposal of the chemical are well described.

Apparently, there are no import-export data for 1,1-DCE. I am not aware of any information that is wrong or missing.

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

This chapter does a credible job in describing the various avenues of potential human exposure to 1,1-DCE, and the extent of its occurrence at NPL sites. I could find no data to add to this.

The text also does an adequate job in discussing the transport, partitioning, transformation and degradation of 1,1-DCE. It also provides levels at which the compound has been detected in the environment and uses the proper units for exposure levels. It also provides information on background levels where they have been measured. I don’t know of any other relevant information.

The text describes sources of potential exposure to 1,1-DCE for the general population as well as occupations handling the substance and of potentially high exposure. I agree with the selected populations – they are well rationalized. I don’t know of any additional populations that should be added to those that are discussed.

CHAPTER 7. ANALYTICAL METHODS

1,1-DCE is routinely analyzed by GC/MS using different detectors to increase sensitivity which is a perfectly acceptable method for volatile compounds at low levels in the environment. This chapter does an excellent job in describing the methods for identifying the compound in different media. These methods should also be applicable for the identification of metabolites of 1,1-DCE. There is a need however, to more sensitively measure 1,1-DCE and its metabolites in human plasma as a biomarker of exposure. Issues related to sampling are addressed in the text.

CHAPTER 8. REGULATIONS AND ADVISORIES

Table 8.1 gives an extensive list of regulations and guidelines for 1,1-DCE from the various government agencies. I have no suggestions of other regulations or guidelines to add to this list. It would be helpful if IARC were to evaluate this compound for carcinogenicity.