THE DOW CHEMICAL COMPANY

MIDLAND, MICHIGAN 48674

1803 BUILDING
May 12, 1989

Mr. Edward J. Skowronski
Assistant Branch Chief, Research Analysis Branch
Agency for Toxic Substances and Disease Registry
Chamblee 28 South
1600 Clifton Road
Atlanta, GA 30333

Dear Mr. Skowronski:

Enclosed are comments of The Dow Chemical Company (Dow) on the ATSDR Toxicological Profile for 1,2-Dichloroethane and 1,1,2-Trichloroethane. These comments are submitted in response to the ATSDR request set forth at 53 Federal Register 51192 (December 20, 1988).

We are pleased to be able to comment on several draft tox profiles from the 2nd priority group of the First List of 100 Hazardous substances. Overall we believe these draft profiles are better written than the drafts for the first priority list were. We are glad to see many of the generic changes recommended to ATSDR have been made in this set of profiles. We hope the tox profiles will be documents that are actively re-evaluated and new data incorporated.

If you have any questions on our comments, please feel free to contact me.

Sincerely,

Richard D. Olson

Richard D. Olson, C.I.H.
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CONFIDENTIAL

cja

enclosure

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EDC Tox Profile file
1,1,2-Trichloroethane file

REV 8(E)

BEFORE THE
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY,
DEPARTMENT OF HEALTH AND HUMAN SERVICES

COMMENTS OF
THE DOW CHEMICAL COMPANY
ON ATSDR'S TOXICOLOGICAL PROFILE FOR 1,2-DICHLOROETHANE

1,2-Dichloroethane Toxicological Profile	Docket No. ATSDR-7
Request for Comment: 53FR51192 December 20, 1988	

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May 12, 1989

COMMENTS OF THE DOW CHEMICAL COMPANY ON ATSDR'S DRAFT TOXICOLOGICAL PROFILE FOR 1,2-DICHLOROETHANE

The Dow Chemical Company (Dow) is a manufacturer of 1,2-dichloroethane or ethylene dichloride (EDC) and submits these comments to ATSDR for the Agency's consideration in preparation of the final profile. We note several changes in the format of the draft that are improvements over previous Profiles. The contractor has adequately reviewed the literature and has produced a well-written draft. Dow scientists have reviewed the draft in detail and have a series of specific comments.

SPECIFIC COMMENTS

FOREWORD (Page iii)

The phrase "(also known as SARA)" should be deleted from the second sentence of paragraph 1, page iii, and inserted in the first sentence of that paragraph after "Public Law 99-499".

In the second sentence of paragraph 1, page iii, "hazardous" should be deleted before "substances" and the following inserted after "substances": "identified as hazardous by CERCLA and SARA".

In the third sentence of paragraph 1, page iii, the term "CERCLA/SARA" should be inserted between "significant" and "hazardous".

These changes improve accuracy and avoid confusion with substances referenced in other environmental statutes and regulations. As revised, the paragraph will read:

The Superfund Amendments and Reauthorization Act of 1986 (Public Law 99-499) (known as SARA) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for substances identified as hazardous by CERCLA and SARA which are most commonly

found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The list of the 100 most significant CERLA/SARA hazardous substances was published in the Federal Register on April 17, 1987.

Section 1.1 (Page 1)

The second paragraph indicates EDC remains in the air for only brief periods, but may remain in water or soil for more than 40 days. This statement may give the mistaken impression that EDC partitions toward soil and water rather than the atmosphere. This paragraph should be revised to indicate the physical properties of EDC dictate it will partition toward the atmosphere where it is readily degraded. Loss from soil and water will be by volatilization with only very slow degradation in soil and water.

Section 1.2 (Page 1)

In the first paragraph (fourth sentence), potential human exposure from uses in the home are mentioned. Most, if not all, of these uses are now obsolete. Exposure potential in the home should be very low. (See our comments on Section 4.3.)

The second paragraph is intended to provide the reader with information on the potential for human exposure via drinking water. As noted in our comments on Section 5.4.2, the most comprehensive drinking water study has been omitted from this report. After inclusion of this important information, a summary should be presented that indicates the percent of samples where EDC was detected, average levels found, and the range. Levels found at hazardous waste sites should be summarized in a separate paragraph to avoid confusion with levels found in general drinking water supplies. The concentration units should be consistent with those used to describe levels producing toxicity throughout the Profile.

The measured concentrations of EDC (range) detected ". . . in the air near highly industrialized areas . . ." should be provided for perspective as was done for reported amounts in drinking water in this section.

The second paragraph provides information on the levels of EDC found in water samples taken at hazardous waste sites. While this is useful information to be included in the Profile, it is misleading to include it in a response to the question: "How might I be exposed to 1,2-Dichloroethane?" without some qualification. Human exposure to EDC from these waste sites will be very infrequent. If this statement is retained, the concentration units should be consistent with those used to describe levels producing toxicity throughout the Profile, and it should be qualified to indicate such exposures will be infrequent.

Section 1.4 (Page 2)

The second sentence indicates EDC caused cancer in animals when eaten. The oral studies were not feeding studies. Administration was by gavage. This section should be revised to indicate the correct mode of administration.

The second sentence in this section reads "assuming that humans respond in the same way as animals, it is possible that humans who eat, drink, or have their skin exposed to high concentrations of 1,2-dichloroethane for a lifetime may develop cancer as well." Environmental exposures near waste sites or elsewhere are likely to be low (ppb, see Section 5). Even industrial exposures tend to be low relative to levels where effects were observed in laboratory animals. Carcinogenicity is not a likely outcome of actual human exposures to EDC. If carcinogenicity is mentioned at all in this section, it should be made clear that such an outcome is extremely unlikely at realistic human exposure levels.

The document states that "Inhalation of 1,2-dichloroethane may also cause cancer." It either needs to be pointed out here that long term inhalation studies of EDC in rats and mice have been negative (Maltoni, *et. al.*, in "Banbury Report 5: Ethylene Dichloride: A Potential Health Risk?", (Ames, *et. al.*, eds) Cold Spring Harbor Press, Cold Spring Harbor, New York, pp. 3-

34.) or the statement needs to be eliminated. In its present form, it is misleading.

The statement "Similar effects have been seen in humans and animals after breathing, eating, or drinking 1-2-dichloroethane" needs additional perspective. It comes right after the discussion on carcinogenicity, and the implication is left that cancer might be one of the similar effects. This statement should start a second paragraph, and the document should clarify the type of similar effects (and the type of exposures necessary) that have been observed.

Section 1.5 (Pages 2 and 3)

This section indicates "examination of expired air is presently the most commonly used technique to determine if a person has been recently exposed to 1,2-dichloroethane".

Since measurement of EDC in expired air is not common at all, a better statement might be "examination of expired air is a potential method to determine if a person has been recently exposed to EDC".

The statement concerning measurement of EDC representing an indication of exposure to other chemicals is sheer speculation and should be deleted from the Public Health Statement.

The statement concerning other medical tests looking "for damage that has already occurred as a result of general chemical exposure" needs to be revised. These tests do not provide an indication of the cause of the damage to human organs.

Section 1.6 (Page 3)

In the fourth paragraph, Minimal Risk Levels (MRLs) are discussed. The reader is referred to Section 2 for information on how MRLs are derived. Since Section 1 is designed to stand alone, it should be made clear in this section that these values are derived by applying safety factors to Lowest

Observed Adverse Effect Levels (LOAELs). It should also be emphasized that the real risk is unknown and, in fact, may be zero.

Tables 1-3 and 1-4, (Pages 6 and 7)

"Levels in food" calculated from other modes of administration should be referred to as "Equivalent ppm."

Section 1.7 (Page 8) and Table 7-1 (Page 94)

Recently OSHA reduced the permissible exposure limit (PEL) from 50 ppm to 1 ppm (8-hour TWA). The proper designation for the OSHA limit is PEL, not TLV. Compliance with this revised PEL is required by September 1, 1989 using any form of control. This should significantly reduce potential worker exposure in the future. Revisions are needed to incorporate these points.

Section 2.2 (Page 10) and Figure 2-1 (Page 18)

The first paragraph, page 10, provides EPA estimates relating to cancer risks. The estimates are referred to as "estimated excess risks" as developed by EPA. EPA does not estimate excess cancer risks. They estimate upper bounds to excess lifetime cancer risks. Reference to such EPA estimates should always be as estimates of the upper bound to excess cancer risk, and they should be qualified, as EPA does with the statement: the true risk is unknown and could be zero.

Section 2.2.1.2 (Page 20)

First Paragraph. The role of glutathione (GSH) appears to be misunderstood in the draft profile. For EDC, conjugation with GSH produces a reactive GSH-conjugate which can bind to cellular macromolecules. See our comments on Section 2.6 for further clarification.

Section 2.2.1.5 (Page 25)

In the last sentence of the second paragraph, it is not clear that the ". . . inaccuracies in the reported results . . ." refers specifically to the Vozovaya (1977) report and not that of Rao, *et. al.* 1980.

Section 2.2.1.7 (Page 26)

The Storer, *et. al.* study should be qualified with respect to the inference of direct genetic damage. The DNA strand breaks reported could have been produced secondarily to tissue injury at the lethal concentrations evaluated.

Section 2.2.1.8 (Page 26)

Suggesting that no conclusions can be drawn from the Maltoni study due to a 78-week duration is inappropriate. Not all strains of rats and mice have high natural survival through two years. Exposure for 78 weeks is without question a significant exposure duration which cannot be dismissed.

In addition, a physiologically-based pharmacokinetic model exists for EDC (DiSousa, *et al.*, 1987--see our comments on Section 2.6 for reference). Internal dose rather than external dose should be integrated into the EPA risk assessment to account for: (1) high to low dose, (2) across species, and (3) across route of exposure extrapolations.

Section 2.2.2.3 (Page 36)

The reduced IgM response reported by Munson, *et. al.* (1982) should be qualified and not considered an unequivocal effect level. The reported response at 4.9 mg/kg/day was nearly equivalent to the control value for the EDC group and, therefore, could have represented biological variation. Furthermore, the lack of response at 189 mg/kg/day for 90 days in the drinking water would support the view that the calculated acute oral MRL of 0.005 mg/kg, which is based on the 4.9 mg/kg/day result, is inappropriately low. Since drinking water exposure is the most relevant route of exposure for

humans, versus gavage (bolus) dosing, MRLs should be based on the drinking water data.

Section 2.2.2.4 (Page 37)

The statement ". . . it is as noxious as gasoline, benzene, carbon tetrachloride, and chloroform when inhaled for periods of an hour or more, and less noxious for shorter exposure periods (Garrison and Leadingham 1954)." should be deleted from this document as this statement is ambiguous and does not accurately define or describe the neurologic effects of EDC.

Section 2.2.2.8 (Page 38)

ATSDR should discuss the results of Klaunig, *et. al.* (Environmental Health Perspectives, Vol. 69, 89-95, 1986) in which EDC was evaluated via the drinking water in an initiation/promotion study. EDC (835 and 2500 mg/l of water) was found not to initiate or promote (phenobarbital-initiated) mouse liver tumors over a 52-week period. While this study itself cannot be considered a "carcinogen bioassay," it does continue to provide support that drinking water administered EDC has markedly less toxicologic activity than comparable, or even lower, gavage-administered doses. The differences likely results from the interplay between the MFO (saturable) and GSH (production of reactive GSH-conjugate) pathways of metabolism, with the route (bolus versus drinking water) of exposure, as described more fully in our comments.

Section 2.2.2.8 (Page 39)

Reference is made to EPA estimates relating to cancer risk. As stated in our comments on Section 2.2, EPA calculations should be described as estimates of the upper bound to lifetime cancer risk with the qualification the true risk is unknown and could be zero.

Section 2.3 (Page 41-46)

This section on relevance to human health should be revised to include a perspective on exposures that cause adverse effects on human health. The

implication of the first paragraph is that EDC produces toxicity to humans exposed in the workplace, in communities where EDC is produced or used, and around waste sites. EDC is controlled in the workplace and the potential for human health effects in communities and around waste sites is very low.

The first sentence in the second paragraph should specifically state the similarity of effects in animals and humans has only been observed following acute exposures.

The last paragraph (page 46) references EPA calculations relative to cancer risk. As recommended above, these estimates should be referred to as estimates of the upper bound to lifetime excess cancer risks, with the note the true risk is unknown and could be zero.

Section 2.6 (Page 48-59)

This section has failed to note some significant work which relates to the development of a physiologically-based pharmacokinetic model for EDC. Specifically, papers on the subject have recently been published by DiSousa, *et. al.* 1) DiSousa, *et. al.*, (1987) "Physiologically based pharmacokinetic model for ethylene chloride and its application in risk assessment; Vol. 8, Safe Drinking Water Series, pp 286-301, National Academy of Science Press, Washington, D.C.; 2) DiSousa, *et. al.*, (1988) J. Pet Exp. Therap., 245, 563-568 (1988). These articles should be reviewed and cited in the ATSDR document.

Section 2.6.1.1 (Page 48)

In the first paragraph, results of a Russian study (Urosova, 1953) are reported. Inhalation exposure to 0.063 ppm in the workplace resulted in increasing levels in breast milk. Based on these numbers, the profile authors conclude that EDC is rapidly absorbed through the lungs by humans. In several places in the profile (Section 2.6.1.3 and 2.5) the validity of these results are questioned since no details on methodology were provided. The results should also be appropriately qualified in this section or the reference dropped.

Section 2.6 (Page 52-53)

In discussing the metabolism of EDC, the authors have not adequately addressed an important aspect of its biotransformation: competition between two different metabolic pathways. As correctly shown in Figure 2.3, EDC may either be oxidized by P450 enzymes or conjugated with GSH through the action of GSH-S-transferases (GST). However, as DiSousa indicates in his papers, the P450 enzymes appear to have a higher affinity for EDC than the GSTs. Consequently, once the P450 enzymes have been saturated, there is a disproportionate increase in the amount of EDC metabolized by the GST pathway. Since metabolites from the GST pathway have been suggested to interact directly with DNA (Rannug, *et. al.*), this may have important implications for extrapolating cancer risk from high doses (above MFO saturation) to environmental exposures (where MFO would not be saturated).

The authors have indicated that metabolic activation is probably involved in the intoxification of EDC. This is almost certainly correct, and an additional statement should be added: "Consequently, the relative rates of metabolic activation in rodents and humans should be considered in making estimates of human risk associated with specific exposures to EDC." This will add valuable perspective for regulators faced with the prospect of deciding whether populations exposed to low concentrations of EDC incur unacceptable increases in health risks.

Section 2.9.2 (Page 62)

As indicated in our comments, a physiologically-based pharmacokinetic model has been developed for EDC by DiSousa, *et. al.* (1987). Such a model will allow for extrapolation across species and routes of exposure. Pharmacokinetic "bridging" must be considered as one evaluates data bases for potential across route of exposure gaps. Physiologically-based pharmacokinetics is a powerful tool which, if applied judiciously, can lead to more effective use of laboratory resources.

Section 2.9.2 (Page 66)

In this paragraph it is suggested that toxicokinetic studies in other species (dogs and nonhuman primates) would be useful to assess more fully any differences among species and the implications for human exposure. Although it would always be helpful to have more data for comparison, the current trend in toxicology is to run fewer tests particularly in higher animals when sufficient data may already exist for comparison.

Section 4.3 (Page 73)

In the second paragraph, a number of uses of EDC are listed. Dow Chemical believes that many of these uses are now obsolete. Dow recommends use as a chemical intermediate and as a solvent only in closed systems. The following uses should be deleted (or indicated as former uses): fumigation, varnish and finish removers, cleaning textiles, extraction and cleaning in organic synthesis, metal degreasing, ore flotation, and in paints, coatings, and adhesives. These obsolete uses should also be removed from Section 1 or indicated as outdated.

Section 4.5.1 (Page 75)

This section indicates a need for information on the amount of EDC disposed of annually. Section 313 of SARA requires the reporting of all emissions and disposal of certain industrial chemicals. Data reported for 1987 should be available from the EPA.

Section 5.1 (Page 77)

In the last sentence in the second paragraph, it is stated that "ingestion of contaminated drinking water and food may also be an important route of exposure for populations living near hazardous waste sites." Data presented later in Section 5 do not really support this conclusion. This sentence should be deleted or a reference provided to support the conclusion.

Section 5.2 (Page 77-78)

This section discusses environmental releases to the various media and quotes 1979 and 1984 data. ATSDR should also check the EPA SARA 313 Emissions database for 1987 production and emissions information and include the more recent data in the profile.

The use of EDC in consumer goods is mentioned as a possible source of release to the environment. EDC is no longer used in consumer goods such as paint strippers or in pesticide formulations, so reference to these uses should be deleted.

Section 5.4.2 (Page 82)

In the second paragraph (last sentence), concentrations of EDC in domestic groundwater supplies ranging from a trace to 400 µg/l are reported. The number of samples affected and the median concentration are unfortunately not presented. It would be appropriate and very useful to include a more recent (1984) and comprehensive study (The Groundwater Supply Survey, J.J. Westrick, *et. al.* Jour. Amer. Water Works Assoc., May 1984). In this study, 945 samples were analyzed. EDC was found in 10 of 945 samples (1.1%) with a range of 0.95 to 9.8 ppb and a median value ranging from 0.57 to 2.9 ppb for the 10 samples in which EDC was found.

Section 5.5 (Page 83)

In the fifth paragraph, it is stated that worker exposure may result from the use of EDC as a grain fumigant. EDC is no longer used in this application. Therefore, potential worker exposure for this application is no longer relevant.

Section 5.6 (Page 84)

The title of the Section 5.6 "Population with Potentially High Exposure" should be changed to "Above-Average Exposure". The use of the word "high" may imply an unacceptable level to some uninformed readers of the

document. Even the highest exposures, presumably in the work environment, are regulated by OSHA and are not high.

The first sentence equates exposure of the general population living in the vicinity of industrial sites or hazardous waste sites with occupational exposure as the highest. Based on the ambient air concentrations near various emission sources presented in Section 5.5 and occupational exposures regulated by OSHA, exposure from ambient air should be far less. Exposures around waste sites should be even lower. This section should be revised to indicate these significant differences in potential human exposure.

Section 6 (Page 87-92)

The analytical section provides an adequate overview of the variety of analytical techniques available for determining EDC in different matrices. However, considering the volatility of this compound, more emphasis should be placed on the importance of precautions necessary during sampling, preservation, and storage of biological and environmental samples to prevent loss from volatilization.