SUMMARY REPORT

OF THE EXTERNAL PEER REVIEW OF THE DRAFT

TOXICOLOGICAL PROFILE FOR

1,4-DIOXANE
Updated Sections

Submitted to:

The Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, MS F-32
Atlanta, GA 30333

Submitted by:

Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

August 6, 2007

QUALITY NARRATIVE STATEMENT

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

TABLE OF CONTENTS

SECTION I

PEER REVIEWERS' SUMMARY COMMENTS

SUMMARY COMMENTS RECEIVED FROM

George Alexeeff, Ph.D.
Deputy Director for Scientific Affairs
Office of Environmental Health Hazard Assessment
California EPA
1515 Clay Street, 16th Floor
Oakland, CA 94612
510-622-3202
E-mail: galexeef@oehha.ca.gov

Peer Review of
Updated Sections of ATSDR's Toxicological Profile for 1,4-Dioxane
(Contract: GS-10F-0036K, Task Order 200-2006-F-17036):
Section 3.2.1: Inhalation Exposure
Section 3.2.1.5: Reproductive Effects
Section 3.3: Genotoxicity
Section 3.4.1.3: Dermal Exposure
Chapter 6: Potential for Human Exposure
Chapter 7: Analytical Methods
Health Advisory

1. Chapter 3. Health Effects

The health effects chapter was reviewed with specific focus on the following updated sections: Section 3.2.1: Inhalation Exposure; Section 3.2.1.5: Reproductive Effects; Section 3.3: Genotoxicity; and Section 3.4.1.3: Dermal Exposure.

Section 3.2.1: Inhalation Exposure;

Were adequately designed human studies identified in the text?

Regarding inhalation exposure, an inhalation study by Ernstgard et al. (2006) was added to the document and used as the basis for calculating the acute inhalation MRL. This study evaluated respiratory effects and subjective symptoms in 12 volunteers following 1,4-dioxane exposure. The study was adequately designed in terms of exposure data, sufficiently long period of exposure to account for the observed health effects, and adequate control for confounding factors.

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

The conclusions drawn by the authors of the Ernstgard et al. (2006) study are appropriate and are accurately reflected in the profile.

Were all appropriate NOAELs and /or LOAELs identified for each study?

The profile identifies 20 ppm (page 26) as a NOAEL for both respiratory and ocular effects in the Ernstgard et al. (2006) study. This was also identified as the NOAEL by the authors of the study. This conclusion is appropriate. The reliability of this NOAEL is fairly high. The major flaw with the

study is that no LOAEL was identified in the study, thus the testing procedures were not fully confirmed.

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?
The statistical tests conducted on this human study (Ernstgard et al. (2006)) were appropriate. Non-parametric testes were used in the analysis. The study authors indicate that the distribution of effects were not consistent with a normal distribution. In that case, non-parametric tests are appropriate. The limitation of the analysis is that the use of non-parametric tests, along with the relatively small number of subjects (12) contributes to the lack of sensitivity of the analysis.

Are you aware of other studies which may be important in evaluating the toxicity of the substance?
No, I am not aware of any other studies at this time.

Are the LSE tables and figures complete and self-explanatory? Are exposure levels accurately presented for the route of exposure?
Yes, the Ernstgard et al. (2006) study has been accurately added to the table for inhalation exposure.

Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?
In general, the assignment of serious and less serious is a consistent with my interpretation of the data. With regard to inhalation exposure, the assignments appear consistent. Less serious effects include eye, nose and throat irritation, serum enzyme changes, while serious effects include death and tissue degeneration. Regarding oral exposure, the assignments appear to be less consistent. Some of the effects reported as less serious in the oral exposure are considered serious in the inhalation exposure. Less serious effects include cellular and tissue swelling, increased tissue weight, blood cell changes, slight weight reduction. But the category also included decreased fetal weight, staggering, cellular necrosis, glomerulonephritis, blood in the urine, hepatocellular degeneration and necrosis, and degeneration and necrosis of tubular epithelium. This reviewer would place these signs in the serious category.

Are the MRLs justifiable?
The MRLs are justifiable and follow standard calculation procedures. The revised acute-duration inhalation MRL is based on the NOAEL of 20 ppm for eye and respiratory irritation and pulmonary

function effects in humans from Ernstgard et al. (2006). The NOAEL of 20 ppm was divided by an uncertainty factor of 10 to account for human variability. The previous MRL acute-duration was also 2 ppm, but it was based on the Young et al (1977) study. In that case, the LOAEL was reportedly 50 ppm, based on eye irritation reported by the subjects. The LOAEL was divided by an uncertainty factor of 30 to account for human variability (10) and to adjust from a LOAEL to NOAEL for a minimal effect (3). The change in the basis of the MRL is justified.

The basis of the acute inhalation MRL was changed to the Ernstgard et al. (2006) study from the previous value developed from the Young et al. (1977) study. The study by Ernstgard et al. (2006) appears to be more reliable than the study by Young et al. (1977) for this purpose. The Ernstgard et al. (2006) study used more subjects than the Young et al. (1977) study; i.e., 12 versus 4. The study of Ernstgard et al. (2006) used male and female subjects while the Young et al. (1977) study utilized only male subjects. The Ernstgard et al. (2006) reported the key response data in the paper while the Young et al. (1977) study did not provide any data. Finally, the Ernstgard et al. (2006) study is of more sensitive design than the Young et al. (1977) study. The previous studies available did not provide sufficient information to verify the conclusions of the authors. Thus, the document bases the acute MRL on the most adequately designed human study available to evaluate this exposure concern.

Have the major limitations of the studies been adequately and accurately discussed?
While the conclusions drawn by the authors of the other human studies in the profile are generally appropriate and are accurately reflected in the profile, I would like to note some remaining exceptions regarding inhalation exposure below:
Regarding Barber (1934), the profile (p. 39, l-4) summarizes the renal effects of 1,4-dioxane exposure. However, the document omits a very significant finding. Each of the cases reported had oliguria and/or anuria, and in one case there was bloody urine. This is an important symptom/sign to note since it clearly corroborates the pathological findings in the kidney and provides information to the public health physician and understandable to the public.
Regarding Johnstone (1959), the profile (p. 39, 4-6) summarizes the renal pathological effects of 1,4-dioxane exposure; however the document fails to mention the development of oliguria. This corroborating sign should be added.
Regarding Young et al. (1977), the profile (p. 38, 11-13) states: "produced no liver alterations as judged by standard clinical chemistry tests (although not specified) and triglyceride determination." This seems to overstate the absence of clinical findings. Young et al. only provides the following information:

> Following the exposure the tests, with exception of the chest X-ray, were repeated at 24 hr and 2 wk. All of the subjects were in excellent health, and no findings related to the exposure were found at either postexposure examination.

The lack of detail (e.g., actual results, method of analysis or statistical information) of any sort makes it difficult to draw a substantial conclusion on this point. Further it does not appear that liver enzymes tests were conducted. Thus to specify that there were "no liver alterations as judged by standard clinical chemistry tests," seems to overstate the published information. I suggest the sentence be rewritten to state: "Exposure of a group of four men to 50 ppm 1,4-dioxane for 6 hours reportedly produced no findings related to exposure (Young et al. 1977)."

Similarly for renal effects (p. 39, 6-8): the profile states: "produced no kidney alterations as assessed by comparing serum creatinine values and urinalysis results obtained prior to exposure with results obtained 24 hours and 2 weeks after exposure." I suggest the sentence be rewritten to state: "Exposure of a group of four men to 50 ppm 1,4-dioxane for 6 hours reportedly produced no findings related to exposure (Young et al. 1977)."

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

The critical effect for the acute MRL development included ocular or respiratory irritation in humans. A sensitive study in laboratory animals for nasal irritation and eye irritation has not been reported. Only the Yant et al. (1930) study reporting much higher exposures in 1930 are available.

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

A bottom-line statement regarding the relevance of eye irritation of respiratory symptoms to human health could not be found by this reviewer.

Are conclusions appropriate given the overall database?

Yes, the conclusions of the Ernstgard et al. (2006) study are consistent particularly with the Young et al. 1977 study. These types of symptoms are consistent with the database in general, including those reported by Silverman et al. (1946) and Fairley et al. (1934). There is inconsistency with the Yant et al. (1930) study, in terms of animal and human responses. It is not clear why the Yant et al. (1930) study is so much less sensitive than the newer studies.

Section 3.2.1.5: Reproductive Effects

Were adequately designed human studies identified in the text?

The profile added two occupation studies that investigated the possibility of reproductive effects in workers exposed to 1,4-dioxane. One study was an investigation by NIOSH (1988) of a plant involving a silk screening process where 1,4-dioxane was one of the solvents used. The other study involved an investigation of 'reproductive outcomes' in pregnant women exposed to 1,4-dioxane in the electronics industry in Russia (Ailamazian, 1990). While these studies are not adequate for in-depth evaluation, they are adequate to include in the profile to provide an overall picture.

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

Yes, the conclusions drawn by the authors of the NIOSH study are limited but appropriate. They are adequately reflected in the profile. The Russian study could not be evaluated since it was a secondary reference. The NIOSH study has been reviewed for the profile and the short summary is appropriate due the limited nature of such investigations. The Russian study has not been directly reviewed but is referenced in an Australian document. The profile clearly notes this. In summary, the new studies are summarized appropriately and accurately in the profile.

Were all appropriate NOAELs and /or LOAELs identified for each study?

No NOAELs and /or LOAELs were identified for either study. The profile does not attempt to identify NOAELs or LOAELs from the studies nor to drawn any substantive conclusions.

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?

Appropriate limited statistical evaluation was conducted in the NIOSH study. It is not known if statistical tests were used in the Russian studies.

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

No, I am not aware of any other studies at this time.

Are the LSE tables and figures complete and self-explanatory? Are exposure levels accurately presented for the route of exposure?

This information was not sufficient to enter into the LSE tables.

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

This information was not categorized as serious or less serious.

Are the MRLs justifiable?

MRLs were not derived from these studies.

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

Yes the limitations of the studies were discussed. While more could be said about the studies, it is reasonable that they are simply included for completeness.

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

Yes, the key endpoint is considered relevant to humans.

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

A bottom line statement was not made. It is suggested that one be added on page 10. Currently page 10 states: "No information was available regarding reproductive, developmental or immunological effects of 1,4-dioxane in humans." This should be revised to incorporate a reference to available information regarding possible effects on reproduction.

Are conclusions appropriate given the overall database?

Yes, the conclusions are appropriate. Unfortunately there are few animal studies evaluating the reproductive toxicity of 1,4-dioxane, but the inclusion of the studies does indicate that further study of reproductive outcomes following 1,4-dioxane exposure appears to be warranted.

Section 3.3: Genotoxicity.

Overall, the genotoxicity summary appears complete and consistent with the data. The profile added two new genotoxicity studies since the previous draft. One study added was conducted by Roy et al. (2005) and investigated chromosome breakage and micronuclei induced by 1,4-dioxane in the bone marrow and liver of young CD-1 mice. The other study added was from McElroy et al. (2003) who evaluated induction of chromosomal aberrations in Chinese hamster cells. In general, the new studies are summarized appropriately and accurately in the profile.

The Roy et al. (2005) study contributes to our understanding of micronuclei formation in mice following 1,4-dioxane administration. The profile discussed micronuclei formation beginning on page 85 (line 31) and carefully discusses this newer study in the context of other available studies. However, I suggest another sentence be added to the Roy et al. (2005) summary. That is, their results "indicate that at high doses, 1,4-dioxane can induce chromosome breakage resulting in micronuclei." This would provide a slightly clearer picture of the state of information in this area. Also I suggest that a paragraph break be placed after on page 88, line 8, prior to "Hepatocytes from Sprague-Dawley rats ..." this would set off the micronuclei information in a separate section which is appropriate since it appears to be one of the most likely genotoxic mechanism for 1,4-dioxane at this time.

The study by McElroy et al. (2003) adds to the previous knowledge that studies in isolated mammalian cells have lead to negative results. The study is cited in the report in this context. No further changes are suggested in the genotoxicity section.

Section 3.4.1.3: Dermal Exposure.

One study newly added (Bronaugh, 1982) evaluated absorption of 1,4-dioxane using excised human skin.

Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance?
The study focused on absorption only. The discussion on dermal absorption on page 90 requires some revision. Two studies evaluated the dermal penetration of 1,4-dioxane. One study newly added (Bronaugh, 1982) evaluated absorption of 1,4-dioxane using excised human skin. This newly added study is summarized appropriately and accurately in the profile. The study reported that occluded skin resulted in a 10-fold increase in absorption, from 0.3 to 3%. The profile does not suggest whether this absorption rate is minimal or excessive, but the impression given, due to the substantial increase by occlusion is that it is substantial. In contrast, when discussing the Marzulli et al (1981) study, the conclusion that less than 4% absorption was minimal. The interesting point is that the less than 4% result of Marzulli et al. (1981) should be compared to the 0.3% in the Bronaugh (1982) study; that is, two studies without occlusion. The two studies together raise the question that dermal exposure of humans to 1,4-dioxane, when occluded, could be substantial. My suggestion in this case would be to remove the words "minimal, being" from page 90, line 24. That would result in an accurate reflection of the information and avoid over-interpretation of the data.

Is there adequate discussion of the differences in the toxicokinetics between humans and animals? What other observation should be made? Is there adequate discussion of the relevance of animal toxicokinetics information for humans?

Some additional discussion, to address the differences in results mentioned above, would be helpful to indicate the potential differences between the animal and human study.

3. 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?

The text has appropriately traced the substance from its point of release to the environment and possible exposures to the receptor population. The profile provides ample information on the release of 1,4-dioxane into the air, water, and soil from those facilities reporting to the Toxics Release Inventory and those facilities covered under the NPL hazardous waste site program. The profile also provides information on the other reported releases that have been published. The document discusses the environmental fate of 1,4-dioxane in terms of transport and partitioning, as well as the transformation and degradation in air, water, sediment and soil. The text describes the levels that have been monitored in the air and water. The profile also provides information on concentrations found in consumer products. Thus, the document has addressed this question to the extent possible for this chemical.

Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites?

Yes, the profile provides sufficient and technically sound information on the extent of 1,4-dioxane occurrence at NPL sites.

Do you know of other relevant information? Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media?

I am not aware of other information in this area.

Does the text provide information on levels monitored or estimated in the environment including background levels? Does the information include the form of the substance measured? Is there adequate discussion of the quality of the information?

The text provides information in this area. The measurements focus on the parent compound 1,4-dioxane. The limited quality of the information is discussed, particularly with regard to the limit of detection and the lack of contemporaneous information.

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? Do you agree with the selection of these populations? Which additional population should be included in this section?

Yes, the profile provides information in these areas. The general population appears to be exposed to very low levels of 1,4-dioxane in the air, water and consumer products. Exposure in the occupational environment is expected to be higher but there is little specific information. There is essentially no information on exposure of children to 1,4-dioxane.

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

I am not aware of any 1,4-dioxane specific data that should be added to the profile.

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

I am not aware on any 1,4-dioxane specific data that should be added to the profile.

Is there discussion of populations at higher risk because of biological differences, which make them more susceptible?

Yes, the profile discusses the likely populations at higher risk because of biological differences, particularly those with compromised liver or kidney function which make them more susceptible. However, these populations are not discussed in the context of exposure. It is expected that their exposures are similar to those of the general population.

<u>Identification of data needs</u>

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

Yes they are presented in a neutral non-judgmental fashion.

Do you agree with the identified data needs?

On Page 161, line 32-33 should be revised as follows: "Information on current and future production and importation levels of 1,4-dioxane are needed to determine whether the risk for human exposure to 1,4-dioxane is significant."

Does the text adequately justify why further development of the data need would be desirable or inappropriate?

Yes proper justification is provided.

2. Chapter 7. Analytical Methods

Are you aware of additional methods that can be added to the tables?

No I am not aware of any additional methods.

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

The document does not discuss methods for measuring key metabolites mentioned in the text. However, reference to the availability of methods is implied.

Identification of data needs

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

Yes they are presented in an appropriate fashion.

Do you agree with the identified data needs?

Yes, they appear to be appropriate.

Does the text adequately justify why further development of the data need would be desirable or inappropriate?

Yes, adequate justification is provided.

Health Advisory

The health advisory clearly states why 1,4-dioxane is a potential health concern and why ATSDR provided the health alert. However, the phrase "clarify confusion" is unclear. Possibly, the statement could read: "During this review, ATSDR developed a Technical Background Document to clarify confusing information resulting from the conflicting reports in the press." In the description of 1,4-

dioxane, it may be confusing to state that 1,4-dioxane is used for "various organic products." This may be associated with the organic designation by USDA. I suggest organic be replaced with "chemical manufacturing," or another more accurate phrase. In addressing how people are exposed I suggest the following revision: "It can also be absorbed through skin following contact with cosmetics, shampoo or bubble bath." Furthermore the last sentence has two "its" which is confusing. The last sentence could read "1,4-dioxane breaks down into other chemicals that quickly leave the body." The description of where 1,4-dioxane is found is clear.

I disagree with the description of health effects from short term exposure. It states: "Symptoms associated these industrial deaths suggest 1,4-dioxane causes adverse nervous system effects." I presume this is referring to the vomiting, but the nervous system is not the issue. I suggest revising to "Symptoms associated these industrial deaths suggest 1,4-dioxane causes adverse kidney and liver effects." Regarding the long-term effects, the statement "Limited evidence suggests that repeatedly breathing small amounts of 1,4-dioxane over long periods of time causes no adverse non-cancer effects in workers," does not appear to be justified. Possibly this is referring to the Thiess et al. (1976) study. However, the study is not included in Table 3-1. One must also be cautious regarding the worker studies and reproductive outcomes. Thus, it would better to state nothing or that "There is little specific information regarding the non-cancer outcomes following repeatedly breathing small amounts of 1,4-dioxane over long periods of time causes in workers." The health advisory makes a statement regarding breast milk transfer. However, I am unable to find the scientific justification for the statement in the profile. I suggest that the index of the profile be revised to clearly indicate where this important information lies.

The comments on medical tests are appropriate.

Regarding levels acceptable by regulatory agencies, the information on cosmetics is unclear. The second bullet states: "The press has recently reported that FDA recommends 10 ppm for 1,4-dioxane in cosmetic products. FDA does not have a recommendation for 1,4-dioxane in cosmetic products." I suggest it be revised to: "While the press has recently reported that FDA recommends 10 ppm for 1,4-dioxane in cosmetic products, the FDA does not have a specific recommendation for 1,4-dioxane in cosmetic products."

Regarding levels in shampoos and bubble baths, the year of the Black study in the note should be included. The section regarding more information appears to be adequate.

SUMMARY COMMENTS RECEIVED FROM

Philip Leber, Ph.D., DABT
Consultant in Toxicology
Akron, OH 44313
330-869-8699
E-mail: toxsci@sbcglobal.net

COMMENTS ON ATSDR TOX PROFILE (DRAFT 2)

1,4-DIOXANE

New inhalation acute MRL

The document indicates that the Ernstgard et al (2006) study should act as the basis for establishing this MRL in lieu of the Young et al (1977) paper. Support for this include:

- The former is a more recent study,
- It includes an objective respiratory endpoint (spirometry), and
- The Young study reported eye irritation at 50 ppm in human volunteers so that study provides a LOAEL, not a NOAEL as does the Ernstgard study. Having a NOAEL is always preferred "point of departure" for establishing safety guidelines.

The one question regarding the Young study is whether the 50 ppm findings should be considered a LOAEL, and not a NOAEL. Two factors need to be addressed: (a) the subjects were not exposed to a 0 ppm control period under same exposure conditions as during dioxane exposures, and (b) the air in the exposure chambers (although not mentioned) may have been dehumidified prior to entry into the breathing zone. Having a baseline for the purported eye irritation is important to establishing the validity of the 50 ppm finding as a LOAE:. This is so because other exposure studies cited in the document reported NOAELs at much higher concentrations of dioxane (e.g., 200 & 2000 ppm), albeit for shorter exposures periods. And finally, low humidity is known to contribute to eye irritation, and if that was employed in the Young study, this factor may have compromised the results.

Validation of the use of the 20 ppm Ernstgard study requires also validation of the Young 50 ppm exposure results as a LOAEL as opposed to being a possible NOAEL.

p.15, 3rd parag, last sentence & A-4, 3rd parag, last sentence. Confusing, needs to be reworded.

Reproductive Effects – Inhalation

It is worth noting in this document the Russian study in which dioxane was reported as one of multiple solvents that may have contributed to the adverse reproductive findings. It is also appropriate to exclude it from Table 3-1 has the study appears to be devoid of estimates of exposure histories for the subjects. The report can make no contribution towards establishing an MRL.

Genotoxicity

This section of the document lists studies conducted, and correctly concludes that the chemical is without significant genotoxic activity. Given that "positive" results were seen only at very high level doses to intact animals, the potential exists for unrelated toxicities contributing to the few positive genotoxic findings reported.

Dermal Exposure

The Bronaugh study indicates that a greater amount of dioxane penetrates human skin under occlusive conditions which is an expected result for virtually all chemicals. The fact that 3.2% of the applied chemical penetrates the *in vitro* dermal specimen should also include a time period during which the penetration was monitored. It also raises the question – how complete was the occlusive covering, and what was the disposition of the remaining 96% of the chemical?

Chapter 6

What is obvious about this chapter is that it is most important to describe the location and potential sources of a chemical in that environment as part of citing data on air concentrations. P.141, 4th paragraph gives ranges for air and water levels of dioxane for US. It makes sense to describe multiple sites within Los Angeles having detectable air levels, but it would be surprising to have any detectable concentrations in the hamlets of Montana. Point is – levels without locations are not helpful.

p. 143-144. "POTW" meaning given in 2nd of the 2 pages (not 1st) where discussed.

p.147, line 2 Text mentions "some environmental media". What are these some?? Would be worth mentioning to indicate what media are assessed in the vicinity of waste sites.

p. 157, line 10 Very doubtful that dioxane is formed from breakdown of ethylene glycol (EG). Since it would take dehydrating conditions for the transformation, more likely it is a contaminant within the original EG product.

p. 158, line 32. Is the use of a 3 kg value for daily diet becoming accepted? Seems very high unless it includes drinking water.

Chapter 7

p.174, line 18. Not sure what the text is suggesting would be useful – new bioindicators of effects? Since the most sensitive effect observed has been eye irritation, what indicator could be hoped for? Similarly, starting on line 30, it is not clear how having sub-ppb analytical sensitivity

would be helpful in determining whether exposure in foods is significant to humans. Given the existing analytical sensitivities for food/food additives and the available toxicological assessments, it is not clear what gains would be had with greater sensitivities.

Otherwise, this chapter is well written, and covers methodologies applicable to assessing human exposures to environmental sources.

SUMMARY COMMENTS RECEIVED FROM

Raghubir Sharma, Ph.D.
Emeritus Fred C. Davison Distinguished Chair in Toxicology
College of Veterinary Medicine
The University of Georgia
Athens, Georgia 60602
706-543-2150
E-mail: rpsharma@bellsouth.net

PEER REVIEW OF THE DRAFT

"Toxicological Profile for 1,4-Dioxane"

Draft 2.

(ERG Task Order 200-2006-F-17036)

Reviewer: Raghubir P. Sharma

Emeritus Fred C. Davison Distinguished Chair in Toxicology

College of Veterinary Medicine

The University of Georgia

Athens, Georgia 60602-7389

Dates reviewed: July 12-July 25, 2007.

The presented draft reads well and includes all the required elements of a "Toxicological Profile" outlined in the guidelines. Only the items indicated in the "Outline of the Updated Section for review...." were reviewed in detail; rest of the draft was casually perused. No editorial comments were needed on the draft and therefore no annotations were required as suggested in the "Guidelines." The added reference to update the acute inhalation MRL is appropriate. The draft is essentially same as reviewed in August 2004 and as published by ATSDR in 2006, with a few additional items and corrections. The comments below refer to the items indicated in "Outline of the Updated Section."

RESPONSE TO SPECIFIC QUESTIONS ON THE UPDATED PROFILE:

Section 3.2.1: Inhalation exposure (beginning page 23)

The newly cited inhalation study by Ernstgard et al. (2006) is first described on page 14 (Section 2.3) where inhalation MRL has been mentioned. The study is further indicated in Table 3-1 (page 26) and the level is also included in Figure 3-1. It is briefly mentioned again on page 36. The description of the study at all locations is adequate and MRL has been correctly derived as also mentioned in Appendix A.

Section 3.2.1.5: Reproductive effects (beginning page 41):

The added paragraph regarding the reproductive effects during occupational exposure is fine and adequately describes the additional information.

Section 3.3: Genotoxicity (beginning page 85):

The two added studies are McElroy et al. 2003 and Roy et al. 2005 are appropriately mentioned on pages 85 and 88, respectively and also included in Tables 3-4 and 3-5, respectively.

Section 3.4.1.3: Dermal exposure (beginning page 90):

Addition of study by Bronaugh 1982 is fine. This is an older reference and does not contribute a lot to the needed information in the toxicological profile for 1,4-dioxane.

Chapter 6: Potential for human exposure: (beginning page 141):

The updated section is adequate for the potential exposure to 1,4-dioxane and describes exposures from the environment such as air, water, soil, etc. The information provided is technically sound. Estimated release of 1,4-dioxane in air has been adequately summarized in the update, along with the statement that 1,4-dioxane has been identified in air samples. Available information on concentration in ambient water is appropriate. Populations that may be exposed to 1,4-dioxane have been identified. The occurrence at the National priorities List (NPL) sites has been provided. The description has appropriately traced the substances from the point of release to the environment until it reaches potentially exposed populations. There is adequate information regarding transport, partitioning, transformation, and degradation of this chemical. The adequacy of data base, particularly the lack of information regarding the levels of 1,4-dioxane in the environment has been discussed. The quality of information available has been described.

Details are provided regarding the general population and occupational exposures. Populations with high exposures have been identified. There is no information regarding exposure to children or general population; the possibilities have been indicated. The need for additional information has been well described.

Chapter 7: Analytical Methods (beginning page 165):

The updating of this section is appropriate. Particularly, the reference of Young et al. 1977 has been omitted from Table 7-1. Table 7-2 has an additional reference of Bozzelli et al. 1980 for

determination of 1,4-dioxane in air. Rest of the section is essentially same as in the previously published toxicological profile for 1,4-dioxane.

Health Advisory:

The information included in this section reads well and is appropriate. Essentially the same information is also summarized in the beginning of the "Toxicological Profile" marked as "PUBLIC HEALTH STATEMENT." It is assumed that this is a separate publication intended as health advisory, particularly as an overview for the public. The document summarizes the reasons for publishing a document on the chemical in question, 1,4-dioxane; what it is, where it is found, the major health effects of this compound, the lack of available medical tests for the exposure to this chemical, acceptable levels of the chemical in environmental media with particular emphasis of the prevalence of 1,4-dioxane in cosmetics, and what can be done to avoid further exposure to 1,4-dioxane. Locations where additional information can be found with a suitable bibliography are added at the end of this brief document.

Specific questions for the revisions:

Is the change in MRL justified?

Yes, with the availability of new NOAEL in humans there is proper justification to revise the acute inhalation MRL.

Are the new studies summarized appropriately and appropriately?

The new studies have been summarized appropriately. There are only a handful of new references; all of these are appropriate and have been adequately described in the document. Some of the new references (Bozzelli et al. 1980, Bronaugh 1982, Ernstgard et al. 2006, McElroy et al. 2003 and Roy et al. 2005) have been indicated in this review above.

Review of the whole document:

Much of the following review of this document is same as provided earlier. All of the deficiencies that were noted in the previous review have been appropriately dealt with; essentially no changes are suggested as indicated again in the following. As mentioned above the rest of the document was perused in general and this reviewer does not have any suggested changes on the text and hence no annotations were made on the draft itself. No marked corrections on the draft are therefore provided.

CHAPTER 1

Public Health Statement:

It is well written in a laypersons' language. The tone of the statement is factual. The information is in a non-technical style suitable for the average citizen. Major headings are stated as questions. The statements are based on the information provided later in the document itself. There are no difficult technical terms in this section.

CHAPTER 2

Relevance to Public Health:

Summary of health effects is appropriately provided in this section. Effects have either been observed or are likely to occur in humans with sufficient exposures to 1,4-dioxane. The exposure conditions are accurately depicted. The effects that have been noticed in humans are similar to those observed experimentally in animals. The target tissue in both humans and animals are same, i.e., liver and kidney, except in cases of exposure via inhalation where irritation (and damage) of respiratory membranes has been reported in humans. A similar effect was reported even in animals given the chemical even via drinking water because of possible exposure of these surfaces during drinking of treated water. The section concerning Minimal Risk Levels (MRLs) is adequate. Tables and figures are clear and understandable. The text is understandable and is based on the information provided later in other sections.

CHAPTER 3

Health Effects:

This section is well written, no changes have been marked as none were deemed necessary. No further changes are indicated and are emphasized with respective headings below.

Section 3.1. Introduction :

It is well presented and includes a brief substance-specific statement. A very brief general introduction has been provided. The health effects have been presented with each route of exposure and in turn effects on different physiological responses or systems are described.

Section 3.2. Discussion of health effects by route of exposure:

The section is generally well prepared. The quantity and quality of human studies is limited. The lack of information is adequately addressed later at the appropriate place in the draft. There are

sufficient numbers of animal studies, which are suitable to derive respective MRLs. The no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse- effect levels (LOAELs) have been identified wherever possible. The discussion via each route of exposure is appropriate. New information regarding the lack of ocular, respiratory and mental effects at 20 parts per million inhalation in humans (Ernstgard et al. 2006), is appropriate to derive the acute inhalation MRL.

Section 3.2.2.2, Systemic Effects

The NOAELs indicated for rats and mice in this section are based on unpublished studies by Japan Bioassay Research Center (JBRC 1998a, b and c). These studies, although have certain limitations as reviewed by this reviewer earlier, are adequate to derive the NOAELs or LOAELs. In these unpublished reports, however, the effective doses were described as ranges (lowest to highest for different individually housed animals). In the profile the mid-point or an average of the lowest and highest levels has been indicated as the NOAEL or LOAEL.

Toxicity – Quality of Human and Animal Studies:

Several case reports where individuals have been either accidentally or occupationally exposed to 1,4-dioxane have been cited and discussed. Although some of the human or animal studies are fairly old and were conducted prior to the introduction of Good Laboratory Practices (GLPs), the studies were apparently properly conducted and reported. There are limited controlled studies in humans and those have been appropriately indicated. The quality of human and animal studies is acceptable. Wherever applicable, the NOAELs and LOAELs are appropriately identified. The statistical tests employed in studies are appropriate.

Level of Significant Exposure (LSE) Tables and Figures:

Tables and figures for the significant exposure are provided in an appropriate way and discussed in the text. The new addition of acute inhalation study in humans (Ernstgard et al. 2006) has provided a revised MRL for this route of exposure. The number of inhalation studies in animals is limited; however, a useful NOAEL could be derived from these studies.

Studies were tabulated as acute, intermediate or chronic exposure. Tables and figures are provided for illustrating exposure conditions and effects. Data from various routes of exposure as indicated in tables was also plotted in figures. Figures are clear and understandable. The LOAELs for less serious and serious effects were rationally classified in tables. The MRLs derived are justifiable.

Evaluation of Text:

The conclusions drawn by the authors for the studies cited are appropriate and accordingly reflected in the text. The limitations of the studies are justifiably described. Effects or key end-points are critically evaluated both for humans and animal studies. The statements related primarily to NOAEL or MRL or other risk level derivations or carcinogenicity potential are acceptable. Conclusions drawn are appropriate based on available data. Limitations of cited studies are accurately reflected in the text. Limited reports of dose-response studies in humans have been described.

Toxicity – Quality of Animal Studies

Limited human data for 1,4-dioxane are available for deriving human MRLs. There are a number of reports on animal effects of 1,4-dioxane. Animal studies reported are of acceptable quality. The data and conclusions from these studies are acceptable. However, data on inhalation and for long-term dermal studies are limited. The deficiency of available information has been accurately described. The rationale for derivation and conclusions drawn from it are adequate. The data needs are identified accurately in the draft. The ongoing research is also summarized.

3.2.2.7. Cancer

The studies have been well described in the text. It is clear from the available animal studies that 1,4-dioxane poses a risk for cancer in humans. The chemical has been recognized as a promoter rather than a genotoxic carcinogen.

3.3. Genotoxicity

Available information on genotoxicity suggests that 1,4-dioxane is not genotoxic. The studies have been well indicated and tabulated.

3.4. Toxicokinetics

This section is appropriate and well narrated. The discussion on the absorption, distribution and elimination after different routes of exposure has been provided. The data available on distribution and organ accumulation are limited via various routes. There is only one study on toxicokinetics of 1,4-dioxane in humans and a few reports in animals after inhalation, and the consideration for these is appropriate. It is possible to predict the dose and species-dependent differences using the physiologically based pharmacokinetic (PBPK) models. No kinetic studies where different constants can be derived are reported for 1,4-dioxane. Available information on metabolism and excretion has been summarized.

A PBPK models for 1,4-dioxane has been developed and validated to a limited extent and the description of this information is adequate. An additional model for humans, rats and mice has been indicated. Various parameters used to develop these models and derived from them are tabulated in Tables 3-6 and 3-7. The units for Vmax and Km are appropriately indicated in Table 3-7.

3.5. Mechanisms of action

The mechanism of toxicity for 1,4-dioxane is not known. The section is adequate and appropriately describes the available information. The lack of information available in this regard has been properly summarized.

3.6. Toxicity mediated through the neuroendocrine axis

This section has the necessary language required. There is no evidence that 1,4-dioxane has significant effect on the neuroendocrine axis.

3.7. Children's susceptibility

The required standard language on this topic was provided in the text of this section. There is no direct information on the sensitivity of children for 1,4-dioxane.

3.8. Biomarkers of exposure and effect

This section is adequately presented. The deficiencies and lack of information has been indicated. The biomarkers of exposure are limited to the presence of 1,4-dioxane and its metabolite β-hydroxyethoxy acetic acid (HEAA) in urine or in plasma.

3.9. Interactions with other chemicals

The description is brief but adequate. The only case report described for possible interaction is totally circumstantial.

3.10. Populations those are unusually susceptible

This section, although largely speculative, is adequate.

3.11. Methods for reducing toxic effects

This section of the report is adequate. No technique for removal from the body is needed because of the short half-life of this chemical.

3.12 Adequacy of the data base

The section is mainly a reiteration of the information provided earlier in the profile. This section has a well-conceived description of available information and deficiencies in the data bases. The existing information and identification of all data needs have been described. Adequacy of data bases and needs for additional information has been indicated. An ongoing study regarding the genotoxic and carcinogenic effect of 1,4-dioxane by Dr. D. A. Eastmond has been indicated. Data needs have been presented in a neutral, non-judgmental fashion and an appropriate identification of data needs has been made.

CHAPTER 4

Chemical and Physical Information:

This section is mainly in the tabular form and adequate. The tables are clear and understandable.

CHAPTER 5

Production, import/export, use and disposal:

There is an adequate description of these items in this section. Facilities that produce, process or use 1,4-dioxane have been tabulated.

CHAPTER 6

Potential for human exposure:

This updated and revised section is well presented and reads well. A general review on this section has been provided above in response to specific questions.

CHAPTER 7

Analytical methods:

All items needed in this section are adequately described in the reviewed draft. Methods for the detection of 1,4-dioxane in biological samples are tabulated along with the detection limits for 1,4-dioxane and its metabolite HEAA. Adequacy of data base, needs for additional information, and the ongoing study to develop methods of analysis have been indicated. Data needs have been presented in an unbiased fashion. Identification of data needs is appropriate. The text adequately justifies the need for further development of data.

CHAPTER 8:

Regulation and advisories:

The draft adequately lists the ATSDR's MRL values via various routes and duration of exposure. The EPA has not developed an RfD for 1,4-dioxane, although it has classified this chemical as a B2 carcinogen. International and national occupational or environmental exposure guidelines are indicated in Table 8-1. The ACGIH and NIOSH recommended TLV and REL for this chemical have been listed in the table.

CHAPTER 9

References:

A comprehensive list of references is included in this section. The references that have been referred to in the draft are appropriately identified with an asterisk.

CHAPTER 10

Glossary

A suitable glossary was appended in the document.

Appendices:

Appendices A, B and C are adequate and appropriate. Appendix A includes the MRL work-sheets; the additional worksheet for acute inhalation MRL is justified. Appendix B is the "User's Guide." It includes adequate description and sample figure for LSEs. Appendix C is the listing of "Acronyms, abbreviations and symbols.

Tables and Figures:

The tables and figures as included with the draft are appropriate.

Supplemental document:

The tables provided as the supplemental document were helpful in checking the validity of numbers included in the text.

Unpublished Studies:

No unpublished studies were included for review and hence this section needs no comments.

Additional References:

No additional references were located in the literatures that are relevant to this document.

Health Advisory

The review on this section has been provided in the beginning of this draft (page 3 above).

PLEASE

INSERT

COLORED

DIVIDER

PAGE

HERE

SECTION II

ADDITIONAL REFERENCES AND DATA SUBMITTED BY THE PEER REVIEWERS

There were no additional publications submitted by reviewers for this review.

PLEASE

INSERT

COLORED

DIVIDER

PAGE

HERE

SECTION III

ANNOTATED PAGES FROM THE DRAFT PROFILE DOCUMENT

ANNOTATED PAGES SUBMITTED BY

George Alexeeff, Ph.D.
Deputy Director for Scientific Affairs
Office of Environmental Health Hazard Assessment
California EPA
1515 Clay Street, 16th Floor
Oakland, CA 94612
510-622-3202
E-mail: galexeef@oehha.ca.gov

In the 2-year inhalation study in rats by Torkelson et al. (1974), hematological parameters were measured in blood collected after 16 and 23 months of exposure. In this study, the rats were exposed to 111 ppm 1,4-dioxane 7 hours/day, 5 days/week. The specific hematological parameters measured were packed corpuscular volume, erythrocyte counts, hemoglobin concentration, and total and differential leukocyte counts. No toxicologically significant deviations from normal limits were found.

Hepatic Effects. Short-term exposure of humans to concentrations that eventually caused death produced serious liver damage. Barber (1934) described five lethal cases in which postmortem examination of the patients revealed an enlarged liver and centrilobular necrosis of the liver cells. Similar lesions were observed in a lethal case described by Johnstone (1959). Exposure of a group of four men to 50 ppm 1,4-dioxane for 6 hours reportedly produced no ~~liver alterations as judged by standard clinical chemistry tests (although not specified) and triglyceride determination~~ (Young et al. 1977). A cross sectional study of 74 workers exposed to concentrations of 1,4-dioxane between 0.006 and 14.3 ppm for an average length of exposure of almost 25 years found no conclusive evidence of serious liver damage (Thiess et al. 1976). Although 6 out of 24 current workers had elevated serum transaminase levels, all 6 were known as habitual alcohol drinkers.

findings related to exposure.

Guinea pigs exposed to acute lethal concentrations of 1,4-dioxane had liver lesions ranging from cloudy swelling to areas of complete necrosis (Fairley et al. 1934). The effect of 1,4-dioxane on the levels of serum ALT, AST, ornithine carbamyl transferase (OCT), and glucose-6-phosphatase was studied in groups of male rats exposed to 0, 1,000, or 2,000 ppm 1,4-dioxane for 4 hours (Drew et al. 1978). The enzyme levels were used as indication of liver damage. Exposure to 1,4-dioxane markedly increased the activities (concentration-related) of AST, ALT, and OCT, particularly 48 hours after exposure. The activity of glucose-6-phosphatase was slightly increased 48 hours after exposure.

A study in which rats, mice, guinea pigs, and rabbits were exposed to 1,000 ppm (the lowest concentration tested) 3 hours/day, 5 days/week for 3–12 weeks reported hepatocyte degeneration of varying severity in all of the species tested (Fairley et al. 1934). In the 2-year inhalation bioassay in rats exposed intermittently to 111 ppm 1,4-dioxane, there was no evidence of any exposure-related gross or microscopic liver alterations or alterations in serum AST and alkaline phosphatase activities (Torkelson et al. 1974). The NOAEL of 111 ppm was used to derive a chronic-duration inhalation MRL of 1 ppm for 1,4-dioxane.

Renal Effects. Swollen kidneys with hemorrhage was seen in subjects who died following exposure to unknown amounts of 1,4-dioxane in the air described by Barber (1934). Microscopic examination showed hemorrhage around the glomeruli with some necrosis. Barber (1934) stated that in at least three of the five cases he described, kidney disease was the direct cause of death. In a fatal case described by Johnstone (1959), postmortem examination revealed necrosis in the kidney cortex with extensive interstitial hemorrhage. Exposure of a group of four men to 50 ppm 1,4-dioxane for 6 hours reportedly produced no kidney alterations as assessed by comparing serum creatinine values and urinalysis results obtained prior to exposure with results obtained 24 hours and 2 weeks after exposure (Young et al. 1977). No evidence of kidney damage was found in a cross-sectional study of 74 workers exposed to concentrations of 1,4-dioxane between 0.006 and 14.3 ppm for an average length of exposure of almost 25 years (Thiess et al. 1976).

Kidney lesions were commonly observed in rodents exposed to acute lethal concentrations of 1,4-dioxane (Fairley et al. 1934). Examination of rats, mice, guinea pigs, and rabbits exposed to 1,000 ppm 1,4-dioxane (the lowest concentration tested) 3 hours/day, 5 days/week for 3–12 weeks, showed varying degrees of kidney damage ranging from vascular congestion to renal cortex degeneration (Fairley et al. 1934). In general, exposure to higher concentrations increased the severity of the effects. In a 2-year inhalation study in rats exposed intermittently to 111 ppm 1,4-dioxane, there were no treatment-related gross or microscopic alterations in the kidneys or significant alterations in blood-urea nitrogen and total protein concentration (Torkelson et al. 1974).

Endocrine Effects. No gross or microscopic alterations were observed in the thyroid and pituitary glands from rats exposed to 111 ppm 1,4-dioxane 7 hours/day, 5 days/week for 2 years (Torkelson et al. 1974). No further relevant information was located.

Dermal Effects. In the 2-year study in rats by Torkelson et al. (1974), the investigators indicated that intermittent exposure to a concentration of 111 ppm 1,4-dioxane in the air had no significant effect on skin condition; no microscopic examination of the skin was conducted. Had skin condition been affected, it would have been most likely due to direct contact with the chemical rather than due to inhaled 1,4-dioxane.

Ocular Effects. In a group of six individuals exposed to 2,000 ppm 1,4-dioxane vapors for 3 minutes in a 10-m^3 chamber, there were no complaints of ocular discomfort (Fairley et al. 1934). Exposure to 300 ppm 1,4-dioxane for 15 minutes produced eye irritation among a group of 12 volunteers (Silverman

marrow cells from CBA mice treated with a single oral dose of 1,800 mg/kg or from C57BL6 mice dosed with 3,600 mg/kg. Studies reported by McFee et al. (1994) of several trials conducted by two different laboratories yielded equivocal results for micronuclei formation in mouse bone marrow. More recent data by Morita and Hayashi (1998) in CD-1 mice treated with a single gavage dose of up to 3,000 mg 1,4-dioxane/kg showed an increase in micronuclei in hepatocytes, but not in peripheral blood reticulocytes. Roy et al. (2005) also reported an increased incidence of micronuclei in hepatocytes and bone marrow from male CD-1 mice treated for 5 days with ≥2,500 mg 1,4-dioxane/kg and ≥1,500 mg 1,4-dioxane/kg, respectively. Hepatocytes from Sprague-Dawley rats dosed with a single dose of 1,000 mg 1,4-dioxane/kg by gavage showed no evidence of DNA alkylation or DNA repair activity (Stott et al. 1981). This dose level administered via the drinking water to the rats for 11 weeks induced minimal hepatocellular swelling, which was accompanied by increased DNA synthesis (Stott et al. 1981). In male Fischer 344 rats administered single doses of up to 2,000 mg 1,4-dioxane/kg by gavage, 1,4-dioxane did not induce replicative DNA synthesis in hepatocytes (Uno et al. 1994), but it did in a subsequent study by the same group of investigators (Miyagawa et al. 1999). In liver tissue from Sprague-Dawley rats given two doses of 2,550 or 4,200 mg 1,4-dioxane/kg, there was a dose-related increase in DNA damage (assessed by alkaline elution) and cytochrome P-450 content; no significant effect was seen at ≤840 mg/kg (Kitchin and Brown 1990). Administration of a single oral dose of 1,000 mg 1,4-dioxane/kg to Fischer 344 rats produced no evidence of hepatocyte DNA repair, and the same negative response was obtained in rats dosed for a week via drinking water containing up to 2% 1,4-dioxane (Goldsworthy et al. 1991). No DNA repair activity was also observed in nasal epithelial cells from rats given 1% 1,4-dioxane in the drinking water for 8 days followed by a single gavage dose of 1,000 mg/kg (Goldsworthy et al. 1991). 1,4-Dioxane did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* in one study (Yoon et al. 1985), but was positive for meiotic non-disjunction in another study in *D. melanogaster* (Muñoz and Barnett 2002).

Collectively, the information available suggests that 1,4-dioxane is a non-genotoxic compound, or at best, a weakly genotoxic compound.

3.4 TOXICOKINETICS

Data in volunteers acutely exposed to vapors of 1,4-dioxane suggest that the chemical is readily and almost completely absorbed through the lungs. Studies in animals also show that 1,4-dioxane is readily absorbed after inhalation and oral exposure, but much less 1,4-dioxane is absorbed through the skin. No information is available regarding distribution of 1,4-dioxane or metabolites in humans. In animals

Young et al. (1978a, 1978b) administered single doses of 10, 100, or 1,000 mg/kg of uniformly labeled ^{14}C-1,4-dioxane exposed to groups of male Sprague-Dawley rats to by gavage for 17 days, and reported that <2% of the label was found in the feces in the first 24 hours (10 mg/kg dose) or 72 hours (100 or 1,000 mg/kg doses), indicating rapid and nearly-complete absorption of the compound from the gastrointestinal tract. In another experimental series reported in the same manuscripts (Young et al. 1978a, 1978b), groups of male Sprague-Dawley rats were given 10, 100, or 1,000 mg/kg of uniformly labeled ^{14}C-1,4-dioxane by gavage daily for 17 days. Less than 2% of the total administered label was recovered in the feces in 480 hours post-exposure, indicating that at least 98% absorption had occurred.

3.4.1.3 Dermal Exposure

Data on the absorption of 1,4-dioxane in humans following dermal exposure are not available, but a study with excised human skin reported that 10 times more 1,4-dioxane penetrates the skin under occluded conditions than under unoccluded conditions (3.2% of the applied dose vs. 0.30%) (Bronaugh 1982). The rate of penetration of 1,4-dioxane in water as vehicle was similar to that in a popular lotion and about 3 times slower than in a lipoidal vehicle, isopropyl myristate (Bronaugh 1982). A lethal case of intoxication with 1,4-dioxane in which the patient had extensive dermal contact with 1,4-dioxane in addition to inhalation of vapors suggests that dermal absorption is possible (Johnstone 1959).

Data in animals are limited to a study by Marzulli et al. (1981) in which uniformly labeled ^{14}C-1,4-dioxane, dissolved in either methanol or skin lotion, was applied to the unoccluded, clipped skin of Rhesus monkeys for 24 hours. The ability of the compound to penetrate the skin was assessed by analysis of radiolabel in the urine. The skin penetration of 1,4-dioxane was ~~minimal, being~~ <4% in all cases; however, because the skin was unoccluded, evaporation may have influenced the study results.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Data on the distribution of 1,4-dioxane following inhalation exposure in humans or animals are not available.

3.4.2.2 Oral Exposure

Data on the distribution of 1,4-dioxane following oral exposure in humans or animals are not available.

Health Advisory - An Overview for the Public

1,4 Dioxane

May 2007

Why is 1,4-dioxane currently a potential health concern?

Conflicting reports regarding 1,4-dioxane exposure from use of some bath and cosmetic products

Recent reports in the media about 1,4-dioxane contamination of children's bath products prompted ATSDR to reexamine its recommendations to families on reducing risks of exposure to 1,4-dioxane. During this review, ATSDR developed a Technical Background Document to clarify ~~confusion given the~~ conflicting reports in the press. The information in this health alert is based on the Technical Background Document. The full technical document is available at : (add link to document when posted). **Note:** The acute effects described in this document are not likely to occur at concentrations of 1,4-dioxane that are normally found in the U.S. environment.

Why has the Agency for Toxic Substances and Disease Registry (ATSDR) provided this health alert for 1,4-dioxane?

ATSDR provides trusted health information to the public.

ATSDR's mission is to serve the public by using the best science, taking responsive public health actions, and providing trusted health information to prevent harmful exposures and disease related exposures to toxic substances.

What is 1,4-dioxane?

1,4-dioxane is used in manufacturing and in household products.

1,4-dioxane (also called dioxane) is produced in large amounts (between 10 million and 18 million pounds in 1990) by three companies in the United States. Companies use dioxane:

- for a solvent for paper, cotton, and textile processing
- for ~~various organic products~~ chemical manufacturing
- in automotive coolant liquid, and
- in shampoos and other cosmetic products.

How are people exposed to 1,4-dioxane?

Transmission through inhalation, ingestion, or skin contact

1, 4-dioxane enters the body when people breathe air or consume water or food contaminated with 1,4-dioxane. It can also be absorbed through skin contact ~~through the use of~~ cosmetics, shampoo or bubble bath. It does not remain in the body because it breaks down into chemicals that are removed quickly.

following with

Where is 1, 4-dioxane found ?

Food	Traces of 1,4-dioxane can be ingested from: • some food supplements • food containing residues from packaging adhesives • food sprayed with pesticides containing 1,4-dioxane as a solvent or inert ingredient
Ground Water	A few communities' water supplies are contaminated with 1,4-dioxane. Information on the concentrations of 1,4-dioxane in groundwater, surface waters and drinking water are limited.
Household products	1,4-Dioxane may be present as a trace contaminant in household products such as: • shampoo • liquid dishwashing soap • baby lotion • hair lotions • bath foam • and other cosmetic products
Industrial solvents	1,4-Dioxane is primarily used as an industrial solvent in several manufacturing processes.
Spermicidal agents	1,4-Dioxane is found in the some over-the-counter spermicidal sponges.

What are the health effects of 1,4-dioxane exposure?

Effects of 1,4-dioxane on human health and the environment depend on how much 1,4-dioxane is present and the length and frequency of exposures. **Note:** The acute effects described below are not likely to occur at concentrations of 1,4-dioxane that are normally found in the U.S. environment.

Short Term exposure to 1,4-dioxane

- Breathing: 1,4-dioxane for short periods of time causes irritation of the eyes, nose and throat in humans. Exposure to large amounts of 1,4-dioxane can cause kidney and liver damage.
- Accidental worker exposure to large amounts of 1,4-dioxane has resulted in several deaths. Symptoms associated with these industrial deaths suggest 1,4-dioxane causes adverse ~~nervous system~~ liver and kidney effects.

Long-term exposure to 1,4-dioxane

- Animal studies: Laboratory studies show that repeated exposure to large amounts of 1,4-dioxane in drinking water, in air, or on the skin causes liver and kidney damage in animals Laboratory studies also show that oral exposure to 1,4-dioxane over a lifetime causes cancer in animals. Skin exposure of animals to 1,4-dioxane has shown that it can increase the cancer-causing properties of other chemicals.
- Human studies: Limited evidence suggests that repeatedly breathing small amounts of 1,4-dioxane over long periods of time causes no adverse non-cancer effects in workers.
- Cancer classifications: (based on inadequate evidence in humans and sufficient evidence in animals):
  - Department of Health and Human Services (HHS) considers 1,4-dioxane as reasonably anticipated to be a human carcinogen
  - Environmental Protection Agency (EPA) established that 1,4-dioxane is a probable human carcinogen.
  - International Agency for Research on Cancer (IARC) has determined that 1,4-dioxane is possibly carcinogenic to humans.

Reproductive Health/infants and 1,4-dioxane

- Miscarriage and still births: Although there are studies that show elevated rates of spontaneous abortion and still births associated with occupational exposure to 1,4-dioxane in combination with other solvents we do not know if this effect is due to 1,4-dioxane alone.
- Breast milk transfer: A nursing mother exposed to a high amount of 1,4-dioxane might pass it to the infant through her breast milk. This concern is based on scientific models, not on actual data from the breast milk of women exposed to 1,4-dioxane.

Is there a medical test to show whether I've been exposed to 1,4-dioxane?

1,4-Dioxane and its 1,4-dioxane and its breakdown products can be measured in your