

**DISPOSITION OF PEER REVIEW COMMENTS FOR  
TOXICOLOGICAL PROFILE FOR 1,4-DIOXANE**

**Agency for Toxic Substances and Disease Registry  
U.S. Public Health Service  
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Peer reviewers for pre-public comment draft 2 of the Toxicological Profile for 1,4-Dioxane were:

Dr. George Alexeeff  
Deputy Director for Scientific Affairs  
Office of Environmental Health Hazard Assessment  
CAL/EPA  
Oakland, California

Dr. Phillip Leber  
Consultant in Toxicology  
Akron, Ohio

Dr. Raghubir Sharma  
Emeritus Fred C. Davison Distinguished Chair in Toxicology  
College of Veterinary Medicine  
University of Georgia  
Athens, Georgia.

ATSDR would like to thank these scientists for their review of the document. When the reviewer's suggestions were followed, or when other revisions obviated the need to respond, no further response is provided herein. Revisions that may have obviated the need to respond included sections that were rewritten, moved, or deleted. Other suggestions made by the reviewers that ATSDR decided not to follow, as well as review comments that needed an explanatory response, are discussed below. In the discussion that follows, "PR" refers to the appropriate page of the assembled peer review document, "P" indicates a page number in pre-public comment draft 2 of the profile, and "L" indicates the line number on that page.

*Review comments provided by Dr. George Alexeeff:*

PR6, T3-2: Dr. Alexeeff says that 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. The reviewer would place these signs in the serious category.

RESPONSE: After reviewing the papers and discussing the histopathological effects with a pathologist, ATSDR agrees to move these effects to the “serious” column in Table 3-2.

PR7-8, P38, L11-13 and P39, L6-8: Regarding the study by Young et al. (1977), Dr. Alexeeff notes that the profile 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 X-ray, were repeated at 24 hr and 2 wk. All of the subject 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. He suggests 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 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.” He suggests 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).”

RESPONSE: The men were given 12 standard clinical chemistry tests and examination of liver enzymes is usually included. The men were also given urinalysis tests. Thus, these sections were rewritten but not exactly as Dr. Alexeeff suggested. Instead, for the liver effects, the text was rewritten as follows: “A group of four men were exposed to 50 ppm 1,4-dioxane for 6 hours and were given 12 “standard clinical chemistry tests” at 24 hours and 2 weeks after exposure (Young et al. 1977). Although the nature of clinical chemistry tests was not specified, there were no effects related to exposure.” For the renal effects, the text was rewritten as follows: “A group of four men were exposed to 50 ppm 1,4-dioxane for 6 hours and were given urinalysis tests at 24 hours and 2 weeks after exposure (Young et al. 1977). There were no effects related to exposure.”

PR15, Health Advisory: Dr. Alexeeff disagrees with the description of health effects from short term exposure. He notes that it states: “Symptoms associated these industrial deaths suggest 1,4-dioxane causes adverse nervous system effects.” He presumes this is referring to the vomiting, but the nervous system is not the issue. He suggest revising to “Symptoms associated these industrial deaths suggest 1,4-dioxane causes adverse kidney and liver effects.”

RESPONSE: The statement regarding adverse nervous system effects is no referring to vomiting. It refers to the neurological effects in the workers who died as described in Section 3.2.1.4 in the Toxicological Profile. Also a statement regarding adverse and liver effects is already included in the previous bullet in the Health Advisory.

PR15, Health Advisory: Dr. Alexeeff notes that he health advisory makes a statement regarding breast milk transfer. However, he was unable to find the scientific justification for the statement in the profile.

RESPONSE: The statement was based on the Fisher et al .(1997) PBPK model, which is discussed in Section 3.4 of Toxicological Profile. Specifically, Fisher et al. (1997) have published a general PBPK model for volatile organic chemicals, which incorporates a compartment for elimination of the chemical in the breast milk. Model simulations predicted a high degree (18%) of lactational transfer of 1,4-dioxane.

*Review comments provided by Dr. Philip Leber:*

PR19, New inhalation acute MRL: Dr. Leber says: 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 LOAEL. 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.

RESPONSE: The text in the profile was revised to indicate “The 50 ppm exposure level constitutes a minimal LOAEL for eye irritation, although there was no control experiment and possible low humidity in the exposure chamber (not addressed in report) might have contributed to the eye irritation.”

PR20, P141, 4<sup>th</sup> paragraph: Dr. Leber says that this 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.

RESPONSE: This paragraph appears in the Overview section of Chapter 6. More specific information on the locations is given in the specific discussion in appropriate monitoring sections in Chapter 6. Therefore, no change was made to the overview.

PR20, P158, L32: Dr. Leber says that the use of 3 kg value for daily diet seems very high unless it includes drinking water.

RESPONSE: The 3 kg value is what the FDA citation indicates and it did not seem to include water. No change was made.

Dr. Leber did not provide any comments on the Health Advisory.

*Review comments provided by Dr. Ragjubir Sharma:*

All of Dr. Sharma's comments were favorable and did not require any revisions to the Toxicological Profile or the Health Advisory.