

September 18, 2000

The Honorable Carol Browner
Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Subject: Comments on "Test Plan for Crude Butadiene C4 Category"

Dear Administrator Browner:

The following comments on the Test Plan for Crude Butadiene are submitted on behalf of People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, Physicians Committee for Responsible Medicine, and Earth Island Institute. These animal protection and environmental organizations have a combined membership of more than nine million Americans concerned with the suffering of animals used in laboratories.

Again, we reiterate the request made in our August 21 letter to you that the EPA respond specifically to our concerns and detail the manner in which the agency intends to ensure that the spirit and the letter of its October 14, 1999, letter to HPV participants are followed. The agency's comments on the first two test plans appear to revert to a "check-the-box" exercise in testing for testing's sake that was specifically proscribed in that October letter. To date, we have not received any response from the EPA on this important matter.

General Comments

The test plan for crude butadiene, submitted by the Chemical Manufacturers Association (CMA) provides a case study in the wide-ranging number of technical and policy issues raised by the high production volume (HPV) chemical-testing program. These issues include:

- The need for coordination among different industries in developing categories of substances in the HPV program.
- The importance of documenting specific tests prior to test plan implementation.
- Compliance with the spirit and letter of guidance provided by EPA to HPV program participants in the form of the October 14, 1999, letter.
- Conducting animal testing for endpoints that are physically, environmentally, or toxicologically irrelevant.



PETA

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- Testing mixed composition industrial streams when they are mixtures of compounds whose toxicity is already well understood.
- The general problem of high interspecies variability in toxicological testing resulting in data providing minimal insight into potential human toxicity.
- Conducting more animal tests on well-characterized compounds with an extensive human epidemiological and toxicological database.

Comments on the Crude Butadiene C4 Category

The CMA Olefins Panel has addressed some of the key issues outlined above. However, this plan also demonstrates the obvious pitfalls of crude, check-the-box toxicological testing, and neglects specific guidance developed for the HPV program by EPA regarding animal testing.

The CMA has done an excellent job of grouping twelve different industrial streams with separate CAS numbers into a single category, recognizing that 1,3 butadiene is the primary bioactive agent in all these mixtures. In addition, in evaluating the potential toxicity of many constituents in these streams, CMA is anticipating coordinating its efforts with other compound groups being developed by CMA and the American Petroleum Institute (API). In reviewing previous test plans,¹ we have expressed concern that this sort of coordination had not occurred. We hope that future test plans will be developed with the cooperation among separate industry consortia that is the case here. Our hope is that this coordination will reduce the number of animals killed in this testing program and we anticipate following the process closely.

One major problem with this test plan is that CMA has provided only a sparse description of the specific test methods it plans to use in conducting “one test battery for all SIDS human health endpoints.” As a matter of fact, the test plan’s executive summary makes no mention of the tests that will be conducted. The plan fails to specifically outline the applicable test methods being proposed, with complete references. Through a review of OECD documents and the robust summaries, we have been able to gain some insight into the specific testing proposed by CMA but we are unable to obtain a complete understanding of all the proposed testing. At a minimum, CMA should identify the exact method it is planning to use for each human health endpoint test, and provide information on whether the tests are *in vivo* or *in vitro*, the species to be used, the exposure method, and the exposure time. For example, the exact method to be used to determine acute toxicity should be clearly stated (e.g., LD-50, fixed dose, up-and-down, acute toxic class).

Further, the proposed test plan ignores the guidance provided in the EPA letter to HPV chemical testing participants dated October 14, 1999. This letter was the result of a negotiated agreement in which the CMA played a key role. This letter states in part:

¹ PETA letter to Carol Browner dated August 21, 2000 (not posted on EPA website as of 9-18-2000).

- “1. In analyzing the adequacy of existing data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Participants may conclude that there is significant data, given the totality of what is known about a chemical, including human experience, that certain endpoints need not be tested.” And,
- “8. As with all chemicals, before generating new information, participants should further consider whether any additional information obtained would be useful or relevant.”

1,3 butadiene toxicity is well understood at both an empirical and biochemical level. These data are well supported by extensive epidemiological data based on worker exposure. Further, the toxicity of other compounds in the crude butadiene streams are well-characterized and are usually much less bioactive than 1,3 butadiene. Despite these facts, the CMA is proposing an extensive set of animal tests to evaluate potential health effects.

As clearly stated in the test plan (Table 2), crude butadiene streams consist primarily of well-characterized simple four carbon compounds. Existing data shows that mid-range butadiene streams are less toxic than one would calculate based on 1,3 butadiene content alone. Yet the CMA is still proposing to conduct a series of animal tests on a stream with an even lower 1,3 butadiene content. This testing is wholly inappropriate and unnecessary.

The additional testing on the low butadiene stream also will provide little useful data for use in regulation, industrial hygiene, or emergency response. The 1,3 butadiene concentration in air is already regulated at very low levels in industrial settings, with a permissible exposure level (PEL) of less than 1 ppm weighted over an 8 hour period. The PEL is based on epidemiological and toxicological analyses of workers and previous animal studies². The crude screening-level tests proposed in this test plan will provide no insight into the regulation of butadiene in the workplace, especially given the extensive toxicological work already being conducted on the metabolism of butadiene in humans^{3,4,5}. Rather, it is the issues of human metabolism of 1,3 butadiene and the resulting cancer-causing mechanism that need further study and evaluation.

Further evidence of the irrelevance of the proposed tests is the acute inhalation toxicity testing for the crude butadiene stream. Existing animal data shows that acute toxicity for

² Material Safety Data Sheet for 1,3 Butadiene. Chemical Safety Associates, Inc. January 23, 1998.

³ M. G. Bird. International Symposium on the Evaluation of Health Risks of Butadiene and Isoprene: General Introduction. Toxicology 113:2-4

⁴ Sathiakumar N, Delzell E, Hovinga M, et al.; Mortality from cancer and other causes of death among synthetic rubber worker. Occup Environ. Med. 55(4) 230-5

⁵ Kohn MC, Melnick RL: .Species differences in the production and clearance of 1,3-butadiene metabolites: a mechanistic model indicates predominantly physiological, not biochemical, control. Carcinogenesis, 1993 Apr;14 (4):619-28

1,3 butadiene occurs at levels between 10% and 13% in air⁶. In general, the other four-carbon compounds in crude butadiene streams also begin to show acute toxicity at similar to slightly higher levels as butadiene (up to 25%)⁷. At these hydrocarbon levels, a large portion of toxicity is simply due to oxygen displacement and asphyxiation. To put these air concentrations in context, 1,3 butadiene is explosive when it is present in concentrations between 2% and 12% in air (it is not explosive above 12% due to reduced oxygen levels). The explosive ranges of other common constituents of crude butadiene streams are between 1.6% and 10%. It is obvious that killing animals to show that they are asphyxiated by a combination of low levels of oxygen and explosive levels of hydrocarbons is not a productive use of CMA's resources. It is also a cruel and pointless waste of animal lives and clearly violates the principles set forth in points no. 1 and 8 of EPA's October 14, 1999, letter to HPV participants.

Further, the EPA's October 14, 1999, letter placed a two-year moratorium on the testing of individual chemicals in order to allow for non-animal test replacements for some SIDS endpoints, specifically acute toxicity testing. Animal protection organizations were assured by the CMA, prior to that agreement, that category testing would limit the number of animals killed and would consolidate information so that acute toxicity testing would rarely, if ever, be proposed for chemicals grouped into categories. We are extremely disturbed that the CMA has not seen fit to abide by the letter or spirit of that agreement, especially in the face of clear existing toxicity data that could easily substitute for more rote "check-the-box" animal testing.

With regard to the carcinogenic and reproductive effects of butadiene, the results of animal testing demonstrate the extremely limited use of animal data in predicting potential effects in humans. Carcinogenic effects in mice have been observed at levels as low as 6.25 ppm butadiene, while some rat studies have shown no carcinogenic effects at levels as high as 8000 ppm butadiene⁸. The differences in response are attributed to significantly different biochemical mechanisms of butadiene metabolism in these closely related species. The variability in the oncological data in rats and mice illustrates the problems associated with applying toxicological data from one species to another even closely related species. The problem is exacerbated when extrapolating from rodents to humans and is best summarized by Cagen *et al.*⁸ (emphasis added):

“Because of the marked species differences in the carcinogenic response to butadiene, estimates of risk vary over **nine orders of magnitude** going from the most sensitive target organ in female mice to less sensitive male rats. An important tool in determining which estimate is most relevant for extrapolation to humans is to ascertain consistency with human experience. Estimated workplace cancer risks which are based on the

⁶ Material Safety Data Sheet for 1,3 Butadiene. Prepared by Chemical Safety Associates, Inc. for Air Products Incorporated. January 23, 1998.

⁷ Material Safety Data Sheets for n-Butane, Isobutane, 1-Butene, cis-2 Butene, trans-2 Butene, and Isobutylene. Prepared by Chemical Safety Associates for Air Products Incorporated. All updated in 1998.

⁸ Cagen SZ, MacDonald RLM, Van Gelder G; Review of risk assessments on 1,3-butadiene (1985-1991). Toxicology 113, 215-220

assumption that humans are as responsive as the mouse suggest added risks of 200 or more out of 1000 workers (1 in 5) exposed to 2ppm butadiene (assume 40 years of exposure). This estimate is clearly inconsistent with what has been seen and this would not have been missed in epidemiological studies."

Carcinogenicity has been the most extensively studied toxic endpoint and these studies show the dramatic differences in sensitivity to butadiene among different species. Because these differences have been partially explained by well-characterized differences in toxicokinetics, it is not surprising that other endpoints show similar disparities. As one peer-reviewed summary notes: "Because the mouse is particularly sensitive to butadiene in comparison with other laboratory species, and there are important functional and anatomical differences between humans and mice, the NOELs and LOELs identified for butadiene for various reproductive endpoints in mice may not be relevant to human reproductive risk."⁹

Despite these cautions, calls for additional testing in mice and rats persist, even though butadiene has been extensively evaluated for reproductive and developmental toxicity in both rats and mice.^{9,10} According to a recent review published in the journal *Toxicology*, the lowest observable effects for developmental toxicity in mice is 200 ppm. It is 1,000 ppm in rats. Reduced testicular weight is seen in mice at 200 ppm and abnormal sperm heads are seen at 1,000 ppm. One apparently infrequently assessed toxicological manifestation, ovarian atrophy, was seen in the same studies that illustrated carcinogenic effects in mice at 6.25 ppm. But the same review notes: "It may be inappropriate to identify the ovary as the target organ for reproductive risk since the ovarian atrophy in mice was identified after completion of the normal reproductive life and after more than 15 months of exposure." Rats exposed to concentrations as high as 8,000 ppm for two years showed no signs of either testicular or ovarian atrophy. Exposure of rats, guinea pigs, and rabbits to concentrations as high as 6,700 ppm for 8 months did not impair fertility.¹⁰

As with cancer, the dramatic species differences between mice and rats in reproductive and developmental effects cast serious doubt on the reliability of either in predicting effects in humans. At the same time, one parallel that may exist is the likelihood that carcinogenicity is the most sensitive endpoint in rats, mice, and humans. The lowest observed effect level in mice and rats is considerably lower for carcinogenicity than for reproductive and developmental effects (with the exception of the above-mentioned ovarian atrophy, identified during the carcinogenicity studies and unlikely to be of relevance). Most importantly studies of exposed workers have consistently shown increased incidences of cancer.

⁹ Christian MS: Review of reproductive and developmental toxicity of 1,3 butadiene. *Toxicology* 1996; 113: 137-43.

¹⁰ Morrissey RE, Schwetz BA, Hackett PI et al.: Overview of reproductive and developmental toxicity studies of 1,3 butadiene in rodents. *Environ. Health Perspect.* 1990; 86:79-84.

The extensive human epidemiological data for butadiene can be used to understand the potential effects and to develop a basis for implementing appropriate workplace exposure levels. Further study of exposed workers, including retrospective studies of workers, could be used to better characterize potential reproductive and developmental effects.

In identifying the hazards posed by crude butadiene streams, we suggest using the tools of risk assessment applied across the country at state and EPA Superfund sites. At these locations, cumulative risk is estimated as a product of a compound's toxicity, exposure to individuals via relevant pathways, and duration of exposure. Using data on the specific composition of different crude butadiene streams, the relative hazard of the different streams could be estimated based on their composition and existing toxicological and epidemiological data on crude mixtures and pure compounds. Uncertainty in these calculations could be accounted for by inclusion of an appropriate safety factor, as is done in CERCLA sites. In fact, an innovative toxicologist may even be able to accurately account for competitive binding of different C4 compounds, a toxicological mechanism mentioned in the test plan that results in lower butadiene toxicity.

This hazard analysis may actually be useful in industrial hygiene and environmental decision-making, because the relative hazard from each of the different members of the group could be ranked. As a hypothetical example, this analysis could provide important input into corporate "Green Chemistry" programs, where the relative toxicity of different butadiene streams could be a factor in choosing a feedstock for a specific chemical manufacturing process. By focusing efforts on interpreting the abundant existing data instead of conducting more animal testing, it is likely that a better understanding of the toxicity of these different butadiene streams would be developed.

Summary

The CMA has developed a costly (both in terms of dollars and animal lives) test plan for butadiene that will provide little information to improve our understanding of the toxicity of crude butadiene streams. Regardless of the outcome of these tests, the handling and emergency response of industrial streams of butadiene will be unchanged, as we already have an extensive understanding of its effects from extensive existing epidemiological data on humans^{11,12}, and an extensive understanding of its physical and chemical properties. The extreme interspecies variability documented by butadiene exposure in animal tests will render these results insignificant relative to our existing understanding of butadiene toxicity based on epidemiological and biochemical analyses. We therefore recommend that the CMA use the massive amount of already existing toxicological data on compounds in crude butadiene streams as the basis for determining the hazards of the members of this group.

¹¹ Acquavella JF, Butadiene epidemiology: a summary of results and outstanding issues. *Toxicology* 113:148-156

¹² Sathiakumar N, Delzell E, Hovinga M, et al.; Mortality from cancer and other causes of death among synthetic rubber worker. *Occup Environ Med* 55(4) 230-5

I can be reached at (757) 622-7382, ext. 304, or by e-mail at jessicas@peta-online.org. Correspondence should be sent to my attention at the following address: 4800 Baseline Road, #E104-390, Boulder, CO 80305. I look forward to your response on this important issue.

Sincerely,

A handwritten signature in cursive script that reads "J.T. Sandler". The signature is written in black ink and is positioned below the word "Sincerely,".

Jessica T. Sandler, MHS
Federal Agency Liaison

cc: The Honorable Robert C. Smith
The Honorable F. James Sensenbrenner, Jr.
The Honorable Ken Calvert
The Honorable Jerry Costello
Council on Environmental Quality