

June 2, 2003

Christine Todd Whitman, Administrator
US Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Comments on the HPV test plan for 2-butene-1,4 diol

Dear Administrator Whitman,

The following are comments on the test plan for 2-butene-1,4 diol (CAS no. 110-64-5) for the HPV program, submitted by the BPPB Consortium on behalf of the 2-butene-1,4 diol Consortium ("the Consortium"). These comments are submitted on behalf of People for the Ethical Treatment of Animals, the Physicians Committee for Responsible Medicine, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These animal, health and environmental protection organizations have a combined membership of more than ten million Americans.

The Consortium proposes conducting a combined repeat-dose, reproductive and developmental toxicity test (OECD no. 421) on 2-butene-1,4 diol. This test will kill at least 675 mammals.

We are concerned that the Consortium is not taking full advantage of existing data on similar compounds, including maleic acid (the analogous carboxylic acid to 2-butene-1,4 diol, which is cited in the plan) and other unsaturated saturated alcohol compounds (e.g., proargyl alcohol), and saturated diols with similar molecular weights (e.g., 1,3 butanediol, 2 methyl 2,4 pentanediol, and 1,4 butanediol). Available maleic acid data is already presented in the test plan. As described in the test plan, 2-butene-1,4 diol is likely transformed to maleic acid during its metabolism. Furthermore, the existing toxicity data for these compounds shows similar behavior with similar observed toxicity levels, and steep dose-response curves once toxic effects are observed. We therefore disagree with the Consortium's claim that the link to maleic acid is weak.

An additional concern with the testing proposal is that the toxicity of 2-butene-1,4 diol is likely to show such high interspecies variability that data generated by additional animal studies will have little relevance to humans. The basis for this statement is the fact that toxicity due to unsaturated alcohols (e.g., 2-butene-1,4 diol) is not usually caused by the alcohols themselves, but by one or more of their metabolites (DeMaster 1994, Cederbaum et al 1981), and the metabolism of similar alcohols differs markedly between species.

In addition, the Consortium should note that an *in vitro* developmental toxicity test, the rodent embryonic stem cell test, is available and suited for a screening level program such as the HPV chemical-testing program. This test has recently become commercially available in the U.S., and last year it was validated by the European



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Centre for the Validation of Alternative Methods, after which the Centre's Scientific Advisory Committee concluded that it was ready to be considered for regulatory purposes (Genschow 2002). We therefore urge the Consortium to keep abreast of progress in this field, and to consider the use of this validated, commercially available and inexpensive non-animal test. We advise the Consortium to correspond directly with the EPA about this issue. We also hope that the Consortium will feel free to contact us for advice about the laboratories that are currently conducting this test.

To conclude, additional animal studies are unlikely to provide any useful information about the human toxicity of 2-butene-1,4 diol. A more useful approach that would result in fewer animal deaths and a more reliable analysis of 2-butene-1,4 diol toxicity would be to carefully develop further analyses of structure activity relationships using existing data from similar compounds and data from *in vitro* tests. Doing so would be consistent with the thoughtful toxicology principles enumerated in the October 1999 agreement to reduce the number of animals killed in the HPV program.

Thank you for your attention to these comments. We can be reached via e-mail at RichardT@PETA.org.

Sincerely,

Jessica Sandler, MHS
Federal Agency Liaison

References

- Cederbaum, A.I., *et al.*, "Role of hydroxyl radicals in the oxidation of alcohols by liver microsomes", *Substance and Alcohol Actions and Misuse* 2: 269-287, 1981.
- DeMaster, E.G., *et al.*, "Comparative oxidation of 2-propyn-1-ol with other low molecular weight unsaturated and saturated primary alcohols by bovine liver catalase *in vitro*", *Chemical Research in Toxicology* 7: 414-419, 1994.
- Genschow, E., *et al.*, "The ECVAM international validation study on *in vitro* embryotoxicity tests: Results of the definitive phase and evaluation of prediction models", *Alternatives to Laboratory Animals* 30: 151-76, 2002.