

201-14897

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December 15, 2003

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Michael O. Leavitt, Administrator  
U.S. Environmental Protection Agency  
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**PETA**

PEOPLE FOR THE ETHICAL  
TREATMENT OF ANIMALS

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Re: Comments on the HPV test plan for thiophene, 3-(decycloxy)tetrahydro-,  
1,1-dioxide

Dear Administrator Leavitt:

The following are comments on the HPV test plan for thiophene, 3-(decycloxy)tetrahydro-, 1,1-dioxide (CAS no. 18760-44-6; termed "thiophene" below), submitted by the American Chemistry Council (ACC). 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 ACC is proposing to conduct an acute fish toxicity test (OECD 203) and a combined repeat-dose, reproductive and developmental mammalian toxicity test (OECD 422). These tests will kill at least 795 animals.

We believe this test plan is fundamentally ill-conceived. Thiophene appears to be of very low acute toxicity: no indications of toxicity were seen in the oral toxicity study in any of the animals tested at doses of up to 10 g/kg – the equivalent of pumping 1.5 pounds of lubricating oil into a human's stomach. The dermal toxicity study also yielded a high LD<sub>50</sub> value (between 4 and 8 g/kg).

This substance provides yet another example of a low toxicity, low solubility compound used as a motor oil additive. Several of these have already gone through the HPV testing process, and they all show similar physical/chemical behaviours, simply resulting from their large molecular size. It is therefore an unfortunate aspect of the HPV that companies feel compelled to check every testing box in the HPV program, even for such a low priority, non-toxic material. The ACC has not provided sufficient justification for killing at least another 675 mammals.

The ACC has also given insufficient attention to the likely modes of exposure. Thiophene is used solely as an additive in lubricating oils in automobiles and other machinery, and the most common exposure scenarios appear to be when people, either professional mechanics or consumers, change engine oils. As the concentration of thiophene in these oils is less than 1%, it is extraordinarily difficult to see how anyone could be exposed to doses remotely approaching those that supposedly resulted in toxicity in the dermal study. In addition, when a low-toxicity substance is so highly diluted, its toxicity is academic, and the issue of concern is the toxicity of the rest of the mixture.

The fact is that additional animal testing on a substance of this nature violates both the October 14, 1999, letter to HPV participants and the December 2000 *Federal Register* notice (Wayland, S.H., Oct. 4, <http://www.epa.gov/chemrtk/ceoltr2.htm>; *Federal Register*, “Data collection and development on HPV chemicals,” Vol. 65, No. 248, Dec. 26, p. 81691) which specifically state that:

*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 sufficient data, given the totality of what is known about a chemical, including human experience, that certain endpoints need not be tested.*

*As with all chemicals, before generating new information, participants should further consider whether any additional information obtained would be useful or relevant.*

In addition, the ACC appears to have made no attempt to estimate the toxicity of thiophene by structural analysis, or to identify related compounds likely to show similar levels or types of toxicity, thus disregarding the EPA’s instruction that “Participants shall maximize the use of scientifically appropriate categories of related chemicals and structure activity relationships” (Wayland 1999, EPA, *Federal Register* 2000). The impression is therefore that the ACC has taken a check-the-box approach to this test plan, with no concern for either the real-world conditions of exposure or the possible types of toxicity.

If the ACC – contrary to all rational and scientific criteria – insists on conducting the OECD 422 as planned, we are officially requesting that the ACC also conduct the rodent embryonic stem cell test (EST) in parallel with the OECD 422. As you are aware, this *in vitro* embryotoxicity test method has been validated by the European Centre for the Validation of Alternative Methods, and the Centre’s Scientific Advisory Committee has concluded that this test is ready to be considered for regulatory purposes (Genschow 2002). We have repeatedly urged individual companies and the ACC to consider the use of this test. We have provided validation and SOP references and suggested that, in this screening level program, a positive result found in the EST should warrant the substance's treatment as a developmental toxicant/teratogen, and that no further testing should then be carried out, again because the HPV program is a *screening level* program.

To date, the EPA has not responded to this issue. However several individual companies have expressed interest in running the EST in parallel with the OECD 421/422. Though doing so will not spare any animals' lives in the current context, it does help build the database for industrial chemicals for eventual validation of the EST in the U.S. To its credit, at least one company has agreed to the extra expenditure of funds to run four of its HPV chemicals through the EST. (You should note that the cost of the EST is a fraction of the cost of the OECD 421/422).

The ACC – as one of the prime architects of the massive animal testing plan that is the HPV program – has a specific responsibility to help with the validation and incorporation of non-animal test methods. We hope to receive a positive response that the ACC will also run the EST

for this substance. We would be happy to provide further information on a local laboratory that conducts this test commercially.

With respect to the proposed fish test, although the ACC states that “no data [were] located” (test plan, p. 5), in fact a study of the toxicity of thiophene to fathead minnows has been conducted previously. The no-observed-effect concentration was found to be 32 mg/L, and the LC<sub>50</sub> concentrations were 55-60 mg/L over 48-96 hours (Swigert 1992). This study was conducted in accordance with GLP, and the results have been filed with the EPA. There is therefore no justification for conducting this additional fish test.

In addition, the log K<sub>ow</sub> value is currently uncertain, and the ACC plans to determine this experimentally (p. 7). The EPA has stated that fish tests are inappropriate for compounds with log K<sub>ow</sub> values above 4.2 (EPA, *Federal Register* 2000, pp. 81679, 81695). At this stage a fish test would therefore be premature, even if fish toxicity data were not already available.

Finally, we note that the ACC plans to carry out an *in vitro* chromosomal aberration assay (OECD 473). This assay is most commonly carried out using Chinese hamster ovary cells. However, human lymphocytes can be used equally readily, and we hope that the ACC will avail itself of this option.

Thank you for your attention to these comments. We would greatly appreciate receiving a response specific to these issues. I can be reached at 757-622-7382, ext 1304 or by email at JessicaS@PETA.org.

Sincerely,

Jessica Sandler  
Federal Agency Liaison

#### References □

EPA, “Data collection and development on high production volume (HPV) chemicals”, *Federal Register*, Vol. 65, No. 248, Dec. 26, 2000.

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.

Swigert, J.P., *et al.*, “Toxicity to fathead minnows, *Pimephales promelas*”, Woodward-Clyde Consultants, Inc., Franklin, Tennessee, EPA doc. no. #86940000905S, Feb. 20, 1992.

Wayland, S.H., Letters to manufacturers/importers, Oct. 4, 1999,  
<http://www.epa.gov/chemrtk/ceoltr2.htm>.