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July 7, 2004

Michael O. Leavitt, 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 the chemical 2,4,6-tris[(dimethylamino)methyl]phenol

Dear Administrator Leavitt:

The following are comments on the test plan the chemical 2,4,6-tris[(dimethylamino)methyl]phenol (CAS# 90-72-2) for the HPV program, submitted by Air Products and Chemicals, Inc. (Air Products). These comments are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, 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.

Air Products proposes to do an OECD 422 screening protocol on this chemical, which will kill approximately 675 animals, and an OECD 473.

First, we want to ensure that Air Products uses either human lymphocytes or mammalian cells obtained from established cultures for its proposed OECD 473, so as to avoid killing additional animals in order to supply the cells.

Second, we have serious concerns with the performance of additional mammalian toxicity testing. The chemical is corrosive and irritating. Rats administered 2,4,6-tris[(dimethylamino)methyl]phenol by oral gavage developed histopathological abnormalities and even hemorrhaging in the non-glandular epithelium of the stomach, hemorrhaging of the small and large intestine, and other effects indicating corrosive damage. Dermal testing reveals the chemical's corrosive nature further; it is characterized as "corrosive" and "highly irritating" in multiple studies. One study was discontinued after 4 days due to the severe skin ulceration observed.

Chemicals that are classified as irritating will not likely cause systemic toxicity at doses that do not also cause significant local GI effects. Thus, the interpretation of any systemic effects that may be observed in proposed reproductive or developmental studies will be confounded by local effects due to the irritancy of the compound. Since it has been

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reported in the developmental toxicology literature that maternal stress may be related to developmental effects, it would be difficult to infer causation in the event of a positive result, since 2,4,6-tris[(dimethylamino)methyl]phenol is so acutely toxic and corrosive. Furthermore, testing lower doses which might avoid the corrosive properties on the GI mucosa is also unlikely to produce any demonstrable toxicity (i.e., reproductive, developmental, or repeat-dose effects).

Additionally, the irritancy potential is such that testing would result in extreme suffering for the animals involved. Other public commenters have pointed out at other times that chemicals with such properties should not be subject to further testing in animals, and the EPA has accepted this principle in its consideration of other HPV test plans on similarly corrosive chemicals. Recent examples include test plans for Benzene and Toluene Sulphonic Acids, submitted by the Aromatic Sulfonic Acids Association in September of 2003, and a test plan for Commercial Hydroxyethylpiperazine, submitted by Dow Chemical Company in December of 2003.

This test plan is a classic example of check-the-box toxicology. We urge Air Products to conduct a thoughtful analysis to determine whether any new testing will result in useful information. Otherwise, the sponsor will be in violation of the EPA-recommended animal welfare principles that state, "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" and "as with all chemicals, before generating new information, participants should further consider whether any additional information obtained would be useful or relevant." (Wayland, 1999, Federal Register 2000).

Thank you for your attention to this issue. We look forward to a prompt and favorable response to our concerns. We can be reached at 202-686-2210 ext. 335 or via email at kstoick@pcrm.org.

Sincerely,

Kristie Stoick, MPH
Research Analyst

Chad B. Sandusky, PhD
Director of Research

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

Wayland SH. Letters to manufacturers/importers. 1999.
<http://www.epa.gov/chemrtk/ceoltr2.htm>.