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May 27, 2003

Christine Todd Whitman, Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Ave., N.W.
Washington, DC 20460

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Subject: Comments on the HPV Test Plan for N-Methylphthalimide

Dear Administrator Whitman:

The following comments on the General Electric Company (GE) High Production Volume (HPV) Chemicals Challenge Program test plan for N-Methylphthalimide (PI) 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 health, animal protection, and environmental organizations have a combined membership of more than ten million Americans.

PI (CAS RN 550-44-7) is one of three test plans submitted by Toxicology/Regulatory Services, Inc. on behalf of GE on December 30, 2002. According to the robust summary, PI is a site-limited intermediate that is made at a single location and used as a reactive intermediate in high molecular weight polyetherimide polymers. GE has proposed performing OECD Test Guideline 422, a combined repeat dose/repro/developmental test on PI, because no adequate data can be found for these endpoints. This test will kill at least 675 animals. For reasons given below, this test should not be conducted.

Neither repeat dose nor reproductive toxicity tests should be conducted without more information being provided on PI production. It is possible, as PI is an intermediate made at a single location in the US, that it may qualify as a closed-system intermediate, although specific information is not given that would allow us to confirm this conclusion. We urge GE to examine this issue as referenced in previous EPA guidance¹ to determine if, in fact, PI qualifies as a closed-system intermediate, and if it does, to submit this information to the EPA.

In addition to the above-mentioned concern, GE has failed to maximize the use of scientifically adequate data in order to minimize further testing in another manner. In its

¹ Statement by the U.S. Environmental Protection Agency (EPA) entitled Guidance for Testing Closed System Intermediates for the HPV Challenge Program, February 8, 1999.

robust summary, GE cites Burdock (1983a), and reports “no adverse effects on any fetal parameters from PI treatment,” (Robust summary p. 43). However, GE states that this developmental study is not completely valid, as only one dose level was used. Actually, two dose levels were used in two separate studies: 500 mg/kg/day in the definitive study and 500 and 1000 mg/kg/day in a previous range-finding study by the same author (Burdock, 1983b). The preliminary study found significant maternal toxicity (death) at the 1000 mg/kg/day level, thus 500 mg/kg/day dose level was selected for the definitive study. Since slight maternal toxicity was found at this dose level (weight loss), it is not necessary to perform another experiment using higher dose levels. Since no developmental effects were found at 500 mg/kg/day, it is also toxicologically senseless to perform another experiment using lower doses to verify a negative developmental effect at maternally toxic levels. Although GE states that maternal toxicity in the form of weight loss was not significantly different from controls, data were not provided that could be used to independently evaluate this statement. Data regarding weight fluctuation during the experiment were also not given, and differences in this parameter could result in different interpretations of such data. Maternal weight loss during a portion of the dosing period may have been significant (due to maternal toxicity) but overall weight gain may have not been significantly depressed at study termination. In addition, even slight weight loss by a pregnant animal can be a sign of toxicity.

Moreover, searching the National Library of Medicine’s TOXLINE database reveals another study regarding the potential teratogenic effects of PI. Lechat et al. (1964), in a study entitled Negative Teratogenic Effects of N-Methylphthalimide, suggests concordance with negative results reported by Burdock (1983a). TOXLINE is a well-known, accepted database, and the failure of GE to include, or even investigate, this study shows their complete lack of concern for the October 1999 agreement and the lives of the 675 animals who stand to suffer greatly should GE continue with its current proposal.

Once again, participants are not following the October 1999 agreement between the EPA, the aforementioned groups, and the chemical industry that states that HPV participants shall “conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Participants may conclude that there is sufficient data...that certain endpoints need not be tested.” The proposal to ignore the available developmental data and suggest new testing is following a checklist approach to the SIDS data requirements.

We once again bring to the EPA’s attention GE’s repeated violations of the October 1999 agreement. Time and time again GE has shown complete disregard for this agreement in submitted test plans, beginning with its first test plan in 2000. This is completely unacceptable toxicology, as are the two other test plans submitted concurrently: 2, 4, 6-Trimethylphenol and 4-Nitro-N-Methylphthalimide. We trust that these comments will be given due attention and that the EPA will give GE guidance regarding both the aforementioned agreement and policies on closed-system intermediates, as well as a direction on how to maximize the use of existing negative developmental data. This will minimize substantially the numbers of animals who will suffer as a result of this program and test plan.

Thank you for your attention to these comments. I look forward to a prompt and favorable response to our concerns. I may be reached at 202-686-2210, ext. 335, or via email at kstoick@pcrm.org.

Sincerely,

Kristie Stoick, MPH
Research Analyst

Chad Sandusky, PhD
Director of Research

References:

Lechat, P., D. Deleau, A. Boime, and O. Bunot (1964) Negative Teratogenic Effects of N-Methylphthalimide. *Therapie* 19:1393-1403.

Burdock, G. (1983a) Unpublished report no 349-267 entitled "Teratogenicity Study in Rabbits, PI BPA-BI, BPA-DA" dated August 25, 1983 for General Electric Company, Pittsfield, MA; USA from Hazleton Laboratories America, Inc., Vienna, VA, USA.

Burdock, G (1983b) Unpublished report no 349-263 entitled "Two-week Pilot Toxicity Study in Rabbits, BPA-BI, BPA-DA, PI and 4-NPI" dated August 20, 1982 for General Electric Company, Pittsfield, MA; USA from Hazleton Laboratories America, Inc., Vienna, VA, USA.