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August 15, 2001

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

Subject: Comments on HPV Test Plan and Robust Summaries for Cyclic Anhydrides Category

Dear Administrator Whitman:

The following comments on the test plan for the cyclic anhydrides category 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 nine million Americans. We again request a response from the Environmental Protection Agency (EPA) to these comments as we have yet to receive a response to any of the 25 test plan comments we have submitted to date over the past year.

The Industrial Health Foundation (IHF) Cyclic Anhydride Committee's test plan for cyclic anhydrides will not expand the current understanding and regulation of the cyclic anhydrides. Although the committee has proposed an appropriate grouping of chemicals with similar structural, physicochemical, and toxicological properties and has submitted robust summaries with some relevant human data, the proposal to conduct an acute fish toxicity test, a repeat dose test, and a reproductive/developmental toxicity test is inappropriate. The cyclic anhydrides and their reaction products are allergenic, corrosive, and blinding. Therefore, further tests on animals will not benefit the environment or public health. Rather, the tests will only provide irrelevant data and cause obvious pain and suffering in animals.

Our concerns with the IHF test plan for the cyclic anhydrides category are as follows:

1. The exclusion of exposure information has led to proposals of irrelevant tests.

2. The exclusion of human health data from the HPV program has resulted in yet another plan for more animal experiments that will not expand the understanding of the public health impacts of the chemical.

3. The test plan violates the following guidelines in the October 14, 1999, letter from the EPA to all HPV participants outlining principles for minimizing irrelevant tests and considering animal welfare:

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

2. Participants shall maximize the use of existing and scientifically adequate data to minimize further testing."

4. Animal welfare considerations, including OECD guidelines, are not being adequately addressed.

5. *In vivo* aquatic toxicity tests are unnecessary, especially given the physicochemical properties of the cyclic anhydrides and the availability of nonanimal aquatic toxicity methods.

**1. The exclusion of exposure information has led to proposals of irrelevant tests.**

The toxic properties of the cyclic anhydrides are well understood. These chemicals hydrolyze readily in the presence of water or moist air and are converted into corrosive diacids. These hydrolysis reactions release toxic, corrosive, or flammable materials that can cause severe injury, burns, or death. Because the cyclic anhydrides and their reaction products cause skin sensitization and ocular corrosive damage at low levels, the cyclic anhydrides are tightly controlled in the workplace. Furthermore, the cyclic anhydrides are not commercially available, and any environmental exposure could only occur if there was an accidental release. Available data already indicates the hazard of such an event.

Exposure data would clarify whether or not these chemicals are sufficiently contained and determine the likelihood of any contact or release of these chemicals. Further toxicity studies are not needed to understand the potential hazards of these chemicals.

**2. The exclusion of human health data from the HPV program has resulted in yet another plan for more animal experiments that will not expand the understanding of the public health impacts of the chemical.**

This test plan reflects a basic flaw of the HPV program: the exclusion of human data. Organic acid anhydrides are associated with mucosal irritation, skin and respiratory sensitization, severe eye irritation, and mild to moderate skin irritation in humans. Sensitization has been noted in various observations and studies of humans. Symptoms of overexposure include rhinitis, conjunctivitis, and asthma-like effects.

The current understanding of the toxicological mechanisms surpasses any information that would be gleaned by conducting any of the SIDS screening level tests. The mechanisms of the allergic response to these compounds in humans have already been explored. In fact, specific serum IgE and IgG antibodies to anhydrides have been documented in workers exposed to these compounds.

**3. The test plan violates the following guidelines in the October 14, 1999, letter from the EPA to all HPV participants outlining principles for minimizing irrelevant tests and considering animal welfare:**

"1. In analyzing the adequacy of existing data, participants shall conduct a thoughtful, qualita-

tive 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.

2. Participants shall maximize the use of existing and scientifically adequate data to minimize further testing."

Human and animal toxicity data are available, and a thoughtful consideration of existing information indicates that additional animal testing would not contribute to the understanding of the potential health and environmental hazards posed by these chemicals. These compounds are known to be sensitizing and corrosive and are therefore already tightly controlled. Additional tests will not change how the chemicals are handled. The major threat to public health and the environment can be attributed to the ability of the anhydrides to cause sensitization and corrosive damage, and these effects have already been explored. Conducting the SIDS battery of tests would not contribute to the understanding of the hazards posed by these chemicals. Extensive work on characterizing the potency, allergic responses, and biomarkers of exposure has already been done. The IHF failed to present many existing studies, some of which are presented in references 1 through 12.[1-12]

Because some companies have failed to consider the physicochemical properties of sponsored chemicals in developing their test plans, testing is being proposed for compounds that are not the relevant toxic moiety, as with the tris(nonylphenol) phosphite test plan submitted by GE as a member of the HPV Phosphite Consortium and the aminosilanes test plan proposed by the Silicones Environmental Health and Safety Council. In its test plan, the IHF is proposing to test the parent compounds, cyclic anhydrides, when the breakdown substances are the actual corrosive and sensitizing agents. All the members of the chemical category hydrolyze readily in water to form corresponding diacids, which are responsible for the major toxic effects of these chemicals. Importantly, for cyclic anhydrides, this degradation reaction is rapid and highly corrosive. Identification of the hazards of the cyclic anhydrides is incomplete without a thorough understanding and presentation of the chemical behavior of these compounds.

In its test plan, the IHF discusses the chemical properties of the cyclic anhydrides and observes that the "solubility of the hydrolysis products and resultant pH is expected to be most relevant in the assessment of potential toxicity. Solubility data for the compounds themselves…is not of much value in the assessment of potential toxicological hazards. Aside from acidic pH resulting from hydrolysis to the diacid, other physical properties do not suggest a potential for environmental or toxicity concerns."

In fact, the only relevant chemical and toxicological properties of these compounds are the acidic and corrosive nature of the reaction that leads to the formation of the diacid of these compounds and the long-term toxicity of the diacid.

**4. Animal welfare considerations, including OECD guidelines, are not being adequately addressed.**

Given the corrosive and irritating nature of these chemicals, repeat dose tests would cause obvious suffering in animals and therefore should not be performed. The corrosive and irritating nature of these compounds is best identified by the pH/pKa data presented in the test plan, where dissolving these compounds in water commonly results in solutions of a pH less than 2.5.

The IHF has especially failed to justify conducting the repeat dose test (TG 408), a 90-day study not even

included in the SIDS battery, and the reproductive toxicity test (TG 415). Proposal of two separate tests is not justified when the combined repeat dose/reproductive/developmental test (TG 422) would reduce the numbers of animals and the study duration. Moreover, the OECD TG 422 combined repeat dose/reproductive/developmental test has already been conducted on one member of the category, MTHPA. The experimental results can be used to extrapolate to other members of the cyclic anhydrides category. Finally, the standard method of dose administration in these tests is orally by gavage. Administration of the cyclic anhydrides to rats via gavage may cause irritation of the forestomach, potentially confounding experimental results.

**5. *In vivo* aquatic toxicity tests are unnecessary, especially given the physicochemical properties of the cyclic anhydrides and the availability of nonanimal aquatic toxicity methods.**

An analysis of the structural and physicochemical properties of the cyclic anhydrides indicates that these chemicals readily hydrolyze in moist soil and water. These substances would not be expected to bioconcentrate in aquatic organisms.

Additionally, *in vivo* aquatic toxicity test methods are available. As described in previous comments, the TETRATOX assay with the protozoan Tetrahymena, can be used as a measure of aquatic toxicity in ecological risk assessments. The biochemistry and physiology of Tetrahymena have been thoroughly investigated since the 1950s, and Tetrahymena, especially *Tetrahymena pyriformis*, have been used for aquatic toxicity testing since the 1970s. Moreover, the genomics of the organism are currently being elucidated. The *Tetrahymena pyriformis* population growth test is quick, easy, and inexpensive and has considerable breadth.[13]

Given both the animal welfare concerns and the need to evaluate the most relevant toxicokinetic chemical moiety, the IHF's test plan is inappropriate for evaluating the toxicity of cyclic anhydride compounds. Conducting additional testing will not increase the understanding of their toxicity, nor will it lead to any change in how these compounds are regulated or managed. It will, however, cause severe animal suffering, which violates the EPA's stated commitment to the reduction, replacement, and refinement of animal use under the HPV program.

Thank you for the opportunity to comment. We would greatly appreciate a response from the EPA, indicating that it is taking these comments into account and is requiring compliance with the standards of the HPV program and the October 1999 letter. I can be reached at 202-686-2210 ext. 302, or via e-mail at <ncardello@pcrm.org>. Correspondence should be sent to my attention at the following address: 5100 Wisconsin Ave., N.W., Suite 400, Washington, DC 20016. I look forward to your response on this important issue.

Sincerely,

Nicole Cardello, M.H.S.
Staff Scientist

## References


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