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July 23, 2004

Michael O. Leavitt, Administrator  
U.S. Environmental Protection Agency  
Ariel Rios Building, 1101-A  
1200 Pennsylvania Ave., N.W.  
Washington, DC 20460

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Subject: Comments on the HPV Test Plan for BISCEP

Dear Administrator Leavitt:

The following comments on Rhodia's test plan for the chemicals BISCEP Monomer and BISCEP Dimer 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.

Rhodia Inc. submitted its test plan on December 23, 2003, for the chemicals Phosphonic acid, (2-chloroethyl)-, bis(2-chloroethyl)ester (BISCEP Monomer, CAS No. 6294-34-4) and Phosphonic acid, [2-{{(2-chloroethoxy)(2-chloroethyl)phosphinyl}oxy}ethyl]-, bis(2-chloroethyl)ester (BISCEP Dimer, CAS No. 58823-09-9). The material, BISCEP, is produced as a mixture of the monomer and the dimer with 55-70% w/w monomer and 35-40% w/w dimer. This mixture is used primarily as an internal chemical intermediate and is produced by a single manufacturer in the U.S. Although Rhodia does not classify BISCEP as a closed system intermediate, we would like to inquire if BISCEP is completely consumed during the production of Ethephon. If this chemical can be classified as a closed system intermediate, the requirement of a repeated dose and reproduction study under the HPV program would be eliminated, thereby sparing the lives of numerous animals. We urge Rhodia to provide the EPA with all the relevant information to support this claim.

At this time, we strenuously object to Rhodia's proposal to conduct a one-generation reproduction study (OECD 415) and an *in vivo* genotoxicity study (OECD 474). If conducted, these tests will result in the death of at least 1,340 animals. If Rhodia wishes to investigate the genotoxic potential of this chemical, the *in vitro* test method (OECD 473) is recommended by the EPA and is adequate for a screening level program such as HPV. EPA clearly states that HPV participants are "encouraged to use *in vitro* genetic toxicity testing to generate any needed genetic toxicity screening data, unless known chemical properties preclude its use (Wayland 1999; EPA Federal Register 2000).

With regard to potential reproductive toxicity of BISCEP, there may not be available data on BISCEP *per se*. However, this is an organophosphate (OP) mixture that is used to produce another organophosphate, the plant growth regulator Ethephon. The OP class of chemicals, as well as Ethephon, has been extensively studied by the EPA and Rhodia acknowledges, on page 3 of the test plan, that there is an extensive database at EPA on this agrichemical. Moreover, there is a two-generation reproduction study on Ethephon where “no effects were observed on fertility, gestation, mating, organ weights or histopathology in any generation” (p. 5 of test plan). OPs, including Ethephon, inhibit cholinesterase activity and have been tightly regulated as posing potential carcinogenic, reproductive, developmental, and neurological hazards. Indeed, the OPs were among the first class of chemicals reevaluated as a group by the EPA under the requirements of the Food Quality Protection Act (FQPA). For the purposes of the HPV program, BISCEP should be treated as another OP and no additional animal testing should be conducted. This approach not only saves the lives of many animals but also demonstrates a thoughtful analysis of the likely toxicity of this chemical based on previous experience with the organophosphate class of pesticides.

Furthermore, data on histopathology of reproductive organs from the repeated dose studies, combined with data from the developmental/teratology study, can be used to meet the SIDS endpoint for reproductive toxicity for BISCEP without conducting additional animal tests. Although histopathology on reproductive organs were not conducted using a traditional study design, we submit that in this instance, the entire knowledge of a chemical, including the extensive data available on other OPs, should be used to determine further planned testing. As indicated in both the October 1999 letter as well as the December 2000 *Federal Register* notice, HPV 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.*”

Finally, we find it unacceptable that Rhodia proposes a one-generation reproduction study when the combined protocol (OECD 421) can be used to meet the SIDS endpoint for reproductive toxicity. Again, EPA recommends that the “combined reproductive and developmental toxicity guideline (OECD 421) be used *in lieu* of separate testing for reproductive toxicity (OECD 415)” (EPA Federal Register 2000). We strongly urge Rhodia to revise their test plan and reconsider their proposal to conduct OECD 415 and 474 simply to “check-the-box” for SIDS endpoints for reproductive and genetic toxicity. Rhodia mentions a Russian study conducted on the toxicity of BISCEP which may be able to address some SIDS endpoints, pending translation of the study. We are hopeful that Rhodia will consider all of these comments and revise their test plan. Thank you for your attention and I look forward to a prompt and favorable response to our concerns. I may be reached at 202-686-2210, ext. 327, or via e-mail at [meven@pcrm.org](mailto:meven@pcrm.org).

Sincerely,

Megha Even, M.S.  
Research Analysis

Chad B. Sandusky, Ph.D.  
Director of Toxicology and Research

### **References**

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