Petroleum HPV

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The Honorable Christie Whitman, Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

ORIGINAL

Attention: Chemical Right-to-Know Program
HPV Consortium #

Dear Administrator Whitman:

The Petroleum HPV Testing Group is a consortium representing 92 percent of the nation's petroleum refining capacity. The Group is made up of 70 member companies of the American Petroleum Institute (API), the National Petrochemical & Refiners Association (NPRA), the Gas Producers Association (GPA) and the Asphalt Institute. The Testing Group appreciates the comments it received on its Test Plan for Petroleum Gases that was submitted to EPA on August 15, 2000 and posted on the Agency's ChemRTK website on September 11, 2000. Both the Environmental Protection Agency (EPA) and the Physicians Committee for Responsible Medicine (PCRM) submitted comments on the Test Plan. In the interest of communicating our intent with all interested stakeholders, the Testing Group is providing a revised Test Plan and robust summaries for posting on the ChemRTK website. In addition, the two documents will also be posted on our website, www.petroleumhpv.org.

To summarize the major issues contained in the EPA and PCRM comments and the Testing Group's responses:

The Petroleum Gases Category
EPA found the submission provided an inadequate basis for accepting such a large group of substances and mixtures as a category. The Agency also found the compositional data on category members to be inadequate. In contrast to EPA, PCRM suggested the test plan made only "minimal use" of categories, and that the Test Sponsors needed to "expand the development" of categories and structure activity relationships. Given the nature of the substances included in this Test Plan, the Testing Group thinks its defined category is appropriate and scientifically justifiable. To clarify this position, the Testing Group has included in the revised Test Plan an expanded explanation of the basis of the Petroleum Gases category, including the compositional range of the category members.

Test Substances Selection and Composition
The EPA noted that the Test Plan needed to include more detailed explanations of the composition of the proposed test samples, how the proposed test substances related to the Petroleum Gases category, and how results from the proposed testing could be extrapolated across the category. In response, the Testing Group has included in the revised Test Plan, expected compositional values of the test samples, a more in-depth rationale for the proposed test substances, how the substances relate to the compositional range of the category members and how test results can be applied to other category members.

Proposed Tests
The PCRM took issue with the Testing Group's plan to perform any testing on these materials. The PCRM believes the use of SAR, data from other Test Plans in the HPV Program and existing data make additional testing unnecessary. Both EPA & PCRM pointed out that three of the proposed test substances have been GRAS listed by FDA, which may limit the need for additional testing.

The Testing Group shares the PCRM's and the EPA's goal that the HPV Challenge Program be conducted in a manner that takes into account animal welfare concerns. In this regard, the Testing Group also shares the PCRM's desire to limit the amount of toxicity testing which is performed under this test plan. However,

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tel: 202-682-8333 • fax: 202-682-8270
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as responsible product stewards, the members of the Testing Group must balance the desire to limit testing with the need to fill essential data gaps. The Testing Group believes it has achieved this balance in the revised Test Plan.

Both the EPA and the PCRM thought that the Testing Group's proposal to perform acute testing on ethane, propane, butane, isobutane, and sweetened LPG (Liquefied Petroleum Gas) would not enhance our understanding of these HPV chemicals. The Testing Group has reconsidered the need for acute testing and agrees with the EPA and PCRM. Consequently, the Testing Group has decided to eliminate the acute, single-dose testing called for in the original Test Plan.

The Testing Group had proposed performing 28- and 90-day repeat dose studies on the individual gases (ethane, propane, butane and isobutane) and LPG, respectively. The individual gases were also to be tested for developmental/reproductive toxicity in separate studies using the OECD 421 protocol. In addition, the developmental toxicity of LPG was to be tested using the OECD 414 protocol. EPA questioned the Testing Group's decision to perform different tests on the individual gases versus LPG, expressing concern that the differences in the studies might make comparison of any results difficult. As an alternative, the EPA suggested that a combined repeat dose/reproductive/developmental screening test (OECD 422) should be performed on all the test samples. The PCRM also questioned the need for separate repeat dose and developmental/reproductive testing, arguing that the combination screening test (OECD 421) is adequate under the HPV program, and should be performed on all the test substances for which developmental/reproductive testing was proposed.

After considering both the EPA and PCRM comments, the Testing Group has revised its original test proposal. The Testing Group has eliminated separate 28-day repeat dose and reproductive/developmental screening studies on each of the individual gases. Instead, combined repeat dose reproductive/developmental screens will be performed on ethane, propane, butane, and isobutane using the OECD 422 protocol. The Testing Group considers this screening protocol to be adequate for the purpose of hazard identification, the goal of the HPV program, while at the same time reducing the total numbers of animals required for testing.

The Testing Group continues to think that because LPG is one of the few substances in this category for which there is the potential for public exposure, more in-depth, extensive testing of LPG is justified. The more robust testing proposed on developmental toxicity for the LPG sample will also provide data required by the EU authorities for their risk assessment of petroleum gases. Therefore, the revised Test Plan still includes a 90-day repeat dose study and a separate developmental toxicity test on LPG. The Testing Group is of the opinion that the combination of screening studies on the individual gases and a full study on a representative commercial mixture (sweetened LPG) is the most efficient and complete way to characterize the potential hazards of petroleum gases.

EPA found that the original Test Plan did not state how the reproductive toxicity endpoint would be satisfied for the sweetened LPG mixture. It is the Testing Group's intent that the 90-day inhalation study being done on the LPG sample will include intensive organ pathology for reproductive tissues. This approach, in contrast to running a separate reproductive toxicity test, will provide adequate screening data and limit the number of animals used in testing. The Testing Group thinks this approach is justified since:

1. LPG will also be tested for developmental toxicity,
2. reproductive/developmental toxicity screens will also be performed on the substances that are the primary components of LPG,
3. a 2-generation reproductive toxicity study has already been performed on a material containing a high percentage of the components of petroleum gases,
4. the major components of the substances in this category are not chemically reactive, and
5. the data set will meet EU risk assessment data needs, thereby avoiding the need for additional testing.

EPA questioned the adequacy of existing *in vitro* genotoxicity data, specifically noting the use in existing studies of methylene chloride as the positive control. The Testing Group considers this a valid concern and has revised the Test Plan to include the performance of the Ames test on all the simple alkane gases and the LPG sample.

The original Test Plan proposed that *in vivo* genetic toxicity tests would be conducted by inhalation on all the test substances in this category (except methane). Both the EPA and PCRM questioned the necessity of doing these tests given the *in vitro* methods that exist for determining chromosomal aberrations. The Testing Group is still of the opinion that the physical/chemical properties of these materials preclude the use of *in vitro* methods for this endpoint. However, in an effort to limit the use of animals, the Testing Group thinks the current HPV SAR criteria will permit the testing of only one substance, with the test results being "read across" to the other alkane gases. Therefore, the revised test plan limits the *in vivo* chromosomal aberration test to one material, sweetened LPG, and incorporates the test into the planned 90-day repeat dose study.

Environmental Fate Issues
The EPA thought the original Test Plan did not provide an adequate justification for the Testing Group's decision not to conduct additional biodegradation studies. The Agency was also critical of the model that the Testing Group had selected for developing environmental transport/distribution data. With regard to biodegradation, the Testing Group is still of the opinion that adequate data exists and consequently there is no need to perform additional tests. To more fully explain its logic, the revised Test Plan includes a proposal to develop a written technical discussion on the physical nature of the alkanes and the fact that their primary route of loss will be to the air compartment where they will degrade through hydroxyl radical attack.

After careful, in-depth review, including contacting outside experts, the Testing Group decided that the use of the model suggested by EPA for evaluating petroleum mixtures transport and distribution behavior is at this time, an inappropriate approach. The Testing Group reached this conclusion due to the lack of accurate emissions data and algorithms estimation limitations based on chemical specific properties.

General Comments
Other comments made by both EPA and PCRM have been addressed in the revised test plan.

Robust Summaries
EPA had a number of detailed comments on individual robust summaries. As appropriate, the attached robust summaries have been revised to respond to these comments.

The Testing Group appreciates the EPA's and the PCRM's comments and interest in the petroleum gases testing program. It believes that the revised Test Plan, being submitted via this letter, is both scientifically sound and meets the spirit of the EPA's guidance on animal welfare. The revised Test Plan makes every effort to minimize the number of animals used in toxicity testing, while at the same time allowing the sponsors to fulfill their product stewardship responsibilities.

If you have further questions or comments about the program, please call me at (202) 682-8344, Tom Gray at (202) 682-8480 or visit our website at www.petroleumhpv.org.

Sincerely,

Lorraine Twerdok, Ph.D.
Petroleum HPV Program Director

Cc:
Karen Florini, Senior Attorney
Environmental Defense

Nicole Cardello, MHS, Research Coordinator
Physicians Committee for Responsible Medicine