

January 9, 2001

Lorraine E. Twerdok, Ph.D., DABT
Manager, Health Sciences
American Petroleum Institute
1220 L Street, Northwest
Washington, DC 20005-4070

Dear Dr. Twerdok:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Petroleum Gases category, sent August 15, 2000. I commend the American Petroleum Institute (API) Petroleum HPV Testing Group for their commitment to the HPV Challenge Program and encourage you to take appropriate steps to make your submission a successful contribution.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Chemical RTK HPV Challenge Program website EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

API has devised a category approach for 161 substances. As detailed in the attached Comments, EPA believes that API needs to better explain the reasons for its approach in such areas as determining the size and boundaries of the category, description of category members, selection of test substances, and showing how the data will be applied to untested category members. Some details of the planned testing are inadequate. The robust summaries for health and environmental effects are also inadequate.

The submission cites the "EPA test rule" as a source of data on 1,2-butadiene and 1-pentene. EPA proposed a test rule for HPV chemicals on December 26, 2000 (FR 65, 81657-81685) which does not include these two chemicals. The test plan needs to address these substances more directly.

As with other submissions where the available data are either inadequate or insufficiently documented, this case will remain open until adequate documentation is in hand.

API proposes to perform *in vivo* studies with five test substances for chromosomal effects (mouse micronucleus assay). In order to conform to the intent of EPA's October 14, 1999, letter to sponsors, which encourages the use of *in vitro* genotoxicity tests unless known chemical properties preclude their use, we ask API to elaborate why it considers *in vivo* testing necessary in this case.

Of the six chemicals proposed for testing, three (butane, isobutane and propane) are listed as Generally Recognized as Safe (GRAS) by the U.S. Food and Drug Administration (FDA). FDA publicly available files may contain toxicity data to support these claims.

EPA will post this letter and the attached Comments on the Chemical RTK web site within the next few days. As noted in the comments, we ask that API advise the Agency, within 90 days of the posting on the Chemical RTK website, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-260-3470. Submit general questions about the HPV Challenge Program through the Chemical RTK web site comment button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submissions and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
C. Auer
M. Weber
A. Abramson

EPA Comments on Chemical RTK Challenge Submission:

Petroleum Gases Category

SUMMARY OF EPA COMMENTS

The sponsor, the American Petroleum Institute Petroleum HPV Testing Group, submitted a Test Plan, Category Justification, and Robust Summaries to EPA. EPA posted the submission on the ChemRTK website on September 11, 2000. The proposed information-gathering plan is for 161 substances and mixtures considered by the sponsor to constitute a category.

EPA has reviewed this submission and found that, in general, the test plan and robust summaries were well-organized and easy to follow. The Agency reached the following conclusions:

(1) The Test Plan does not support the proposed information gathering on these chemicals as a category. The submission provides an inadequate basis for accepting such a large group of substances and mixtures as a category, compared to other possible approaches.

(2) The mixture definitions provided do not describe adequately the possible composition ranges of these category members. See Category Definition comments.

(3) The test substances insufficiently represent the range of constituents of the mixtures in the category. None of the test substances contain inorganic or thiol constituents. The sponsor does not explain why testing only one mixture (in addition to the five single chemical test substances) is adequate. Carbon numbers higher than C5 are not accounted for in the plan.

(4) The sweetened liquified petroleum gas (LPG) test substance is inadequately defined. See Test Plan comments.

(5) The submission inadequately addresses the presence of inorganic constituents in the various mixtures in the category. While inorganic substances themselves are generally excluded as Challenge program candidates, HPV substances containing inorganics need to be characterized fully, or the lack of a complete characterization must be justified adequately.

(6) No "category matrix" or equivalent analysis of potential data extrapolation to non-tested category members was provided. See Test Plan comments.

(7) The testing summary table does not reflect the sponsor's stated intention to calculate ecotoxicity values.

(8) Environmental Fate. (a) Biodegradation: the sponsor fails to justify adequately not performing laboratory studies for this endpoint; see Test Plan comments. (b) Transport/distribution modeling: the sponsor used EQC Level I. EPA recommends using the EQC Level III model from the Canadian Environment Modeling Centre at Trent University. This model can be found at the following Web address: <http://www.trentu.ca/academic/aminss/envmodel/>.

(9) Health Endpoints: Test Plan. There is insufficient rationale for the following portions of the test plan: (1) excluding methane from the proposed testing; (2) proposing different test protocols for the individual gases versus the sweetened LPG mixture; and (3) not including an Ames test or equivalent for ethane.

(10) Health Endpoints: Robust Summaries/Additional Information. The submitted robust summaries are inadequate for the purposes of the U.S. HPV Challenge Program.

(11) Environmental Effects. The sponsor needs to supply additional composition information on category members. Calculated or measured toxicity data for substances with carbon number higher than C5 and for inorganics need to be included as appropriate for the category.

Because of the complex nature of this submission and of these comments, EPA requests that the Sponsor advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON THE PETROLEUM GASES CATEGORY CHALLENGE SUBMISSION

EPA's comments are organized as follows: Category Definition; Category Justification; Test Plan; Specific Comments on Robust Summaries.

Category Definition

The submission presents a case for 161 substances that are mostly variable-composition mixtures containing different combinations of up to 33 different hydrocarbons (Table 1 of the submission), and for at least 59 of the 161 substances an additional one to four inorganic constituents. Table 2 of the submission shows that 19 of the 33 hydrocarbons are HPV chemicals.

The sponsor correctly states that the way in which petroleum gas mixtures are produced precludes defining exact percentages of constituents. Nonetheless, in most cases the mixture definitions provided do not describe adequately the possible composition ranges of the category members. The sponsor is referred to the Crude (High) Butadiene C4 submission from the ACC Olefins Panel for an example of such mixture characterization.

Some mixture definitions (Appendix I) include C6 or C7 components but no substances above C5 are identified in Table 1, Hydrocarbon Constituents.

The sponsor states that 153 of the 161 category members are HPV chemicals but doesn't identify the eight non-HPV chemicals. EPA identified five as not on the HPV list (CAS Nos. 68308-02-1, 68308-09-8, 68475-57-0, 68527-14-0, 68919-00-6). To avoid confusion and permit confirmation by reviewers, the sponsor needs to identify the non-HPV members by CAS number.

It is unclear why API combined in its category those gas streams that contain inorganics with those that do not. From the descriptions of the substances provided in the Test Plan, EU category #2 cited in the submission contains the six chemicals API plans to test, with only 10 of the 112 chemicals in that EU category containing inorganics, while 49 of 49 chemicals in EU category #35 have inorganic constituents. Thus, 59 of the 161 have inorganic constituents. The major inorganic component of these substances appears to be hydrogen, but such inorganics as carbon monoxide, hydrogen sulfide, ammonia, nitrogen, and carbon dioxide frequently appear as significant members. At one extreme, Gases (petroleum), ammonia-hydrogen sulfide, water-saturated (CAS No. 68783-05-1) contains up to 30% hydrogen sulfide and up to 60% ammonia. CAS No. 68919-01-7 (Gases (petroleum), distillate unifiner desulfurization stripper off) includes hydrogen sulfide, methane, ethane, and propane. and CAS No. 68989-88-8 (Gases (petroleum), crude distillation and catalytic cracking) contains hydrogen, hydrogen sulfide, nitrogen, carbon monoxide and paraffinic and olefinic hydrocarbons.

An incorrect CAS number is ascribed to 2-methylpropane on page 8 of the Test Plan. The correct CAS number for 2-methylpropane is 75-28-5.

Category Justification

EPA believes that the sponsor has not provided an adequate basis for accepting a large, varied group of substances and mixtures as a category or demonstrated the validity of the extrapolation approach for these substances. Because the size of the category raises obvious questions, the sponsor needs to provide a more developed justification for its approach. For example, is it possible to simplify the analysis by dividing the category into smaller groups of more closely related substances? Doing so might address many of the questions raised in the next section of these comments.

Test Plan

The Test Plan does not adequately support the proposed information gathering on these chemicals as a category.

The sponsor's submission (1) identifies five individual gases (methane, ethane, propane, butane, 2-methyl propane) for which they will gather data to represent those constituents of the mixtures in the category not being tested by other sponsors; (2) proposes to use data generated on these chemicals plus data from testing carried out by other sponsors or programs on other mixture constituents to evaluate effects of category members; (3) proposes a variety of toxicity tests on four of the five individual gases (excluding methane); and (4) proposes to test one mixture (sweetened Liquefied Petroleum Gas (sweetened LPG), CAS # 68476-86-8) to represent all other mixtures in the category.

Evaluation of the category proposal is impeded because the sponsor did not provide a matrix, as described in the EPA guidance document on *Development of Chemical Categories in the HPV Challenge Program* (<http://www.epa.gov/opptintr/chemrtk/guidocs.htm>) showing how the category members will be characterized relative to the chemicals for which data will be generated. Such a matrix would be less unwieldy for petroleum gases if similar streams could be grouped for this purpose. Unfortunately, the test plan leaves it to the reader to determine which of the mixtures might have such similarity.

The proposed testing (including that by other sponsors and programs) will likely cover nearly all the individual HPV constituents listed separately as category members. However, the mixture test substance, sweetened LPG, is described only in very broad terms. It references "EU requirements" for the substance without describing these further. The sponsor needs to state what the specific composition of this substance will be, at least within limits that will permit reviewers to understand what is being tested and to judge whether the proposed mixture is a reasonable representative of all the mixtures in the category. As described in the text, the material could contain significant or insignificant amounts of hydrocarbons in the C5–C7 range. Yet the sponsor's reference to meeting the ASTM standard for Commercial Butane-Propane Mixtures suggests the test substance will contain no more than 2% C5 and higher, while many of the mixtures in the category contain C5 and C6 components, and a few contain C7.

The choice of test substances ignores the presence of inorganic constituents in the various mixtures in the category. While inorganic substances themselves are excluded from the Challenge program HPV list or designated as non-candidates, HPV substances containing inorganics need to be characterized fully, or the lack of a complete characterization must be justified adequately. Labeling such constituents "non-Challenge chemicals" (p. 8 of the test plan) is not an acceptable justification. While the test plan indicates the intent to use "existing data on inorganic substances," it does not discuss how adequate those data are. Because these are not HPV Challenge chemicals, no robust summaries are expected in the context of individually sponsored chemicals although for the physicochemical data endpoints the sponsor states (test plan, p.11) that data for inorganics will be added to the summaries as appropriate. This could be acceptable if data adequacy is addressed satisfactorily.

The test substances may not adequately represent the range of constituents of the category members. For example, the only test substance that is a mixture does not contain any of the inorganic or thiol constituents reported for many of the category members. Furthermore, the sheer number of substances in the category suggests at first glance that more than one test substance should be a mixture, in order to confirm the sponsor's apparent presumption of additive toxicity for the constituents. The submission devotes no significant discussion to this issue. As stated in a previous paragraph, it is unclear how representative the sweetened LPG mixture will be of the full range of just the hydrocarbon constituents. The sponsor needs to provide a fuller, more coordinated discussion of these issues.

The text indicates that the sponsor will calculate ecotoxicity values using the ECOSAR program, but the table on page 14 does not reflect this. Especially in the case of category submissions, many readers will rely heavily on such tables for basic test plan information. The table needs to be revised to indicate where technical discussions will include estimated data or other types of information collection.

On page 8 of the submission the sponsor points to other expected test plans as sources for some of the

data for chemicals in this category, and further cites the “EPA test rule” as a source of data on 1,2-butadiene and 1-pentene. A proposed test rule for HPV chemicals appeared on December 26, 2000 (FR 65, 81657-81685) and does not include these two chemicals. The test plan needs to address these substances more directly.

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)

The sponsor’s approach to the physicochemical endpoint results for the category is incomplete. The submission suggests that the data on methane, ethane, propane, butane, and 2-methylpropane presented in the robust summaries will sufficiently cover the range of properties found in the 161 test substances. They note that where inorganic chemicals are present in sufficient quantities to affect the physical or chemical properties, data for the inorganics will be added to the robust summaries. The test substances may not span the range of chemicals present in the 161 substances even with the addition of the chemicals listed in Table 3 of the test plan, according to the definition of the mixture test substance (see EPA comments on mixture test substance description under Test Plan).

Fate (photodegradation, stability in water, biodegradation, and transport/distribution)

The sponsor’s approach to generating data for the fate endpoints is acceptable in part. However, the application of the category approach may be inadequate.

The argument that use considerations suggest that these chemicals are unlikely to enter the environment has little basis. While the major portion of the 161 substances under consideration in this Test Plan are mainly used as refinery feedstocks (and hence do not have the same potential for entering the environment as commercially available substances), the test data generated under this Test Plan will likely be used in support of various testing and assessment activities. For example, the Test Plan requires, at a minimum, the results of testing from the Olefins Panel, Hydrocarbon Solvents Panel, Mercaptans/Thiols Council, OECD/SIDS Program, and EPA test rule on HPV chemicals (Table 3 of the Test Plan), and it is likely that the results of the Petroleum Gases Test Plan will be required by other test plans that consider commercial non-feedstock products.

Finally, no accounting or consideration is made for the additional members of the 161 substances not covered by the Test Plan or referenced test plans, including such chemicals as benzene, hexanes, heptanes, ammonia, and hydrogen sulfide. The environmental behavior of these chemicals will be very different than the test substances under consideration in this Test Plan.

Photodegradation – The submitter notes that photooxidation will be the most important atmospheric removal process. They also note that the information on photooxidation presented in the robust summaries cannot be confirmed. Because of this, the submitter states that AOPWIN calculations will be performed for methane, ethane, propane, butane, and 2-methylpropane. Again, this range of chemicals will not adequately span the range of chemicals in the 161 substances even with the addition of data expected for chemicals from other plans or programs. Many of the hydrocarbons present in these substances are outside the range of chemicals considered for testing and no accommodation is made for the inorganics present. These chemicals should be accounted for in some way or considered for treatment in a separate test plan(s).

Stability in Water – The submitter suggests that since none of the chemicals considered for testing contain any hydrolyzable groups, the testing requirement will be met with a technical discussion. This and similar technical discussions should be written to clearly apply to all the chemicals present in any of the mixtures and not just the test substances.

Chemical Transport and Distribution in the Environment – For fugacity modeling the sponsor used EQC Level I. EPA recommends using the EQC Level III model from the Canadian Environment Modeling Centre at Trent University. This model can be found at the following Web address: <http://www.trentu.ca/academic/aminss/envmodel/>.

While this approach is reasonable for the compounds under consideration (methane, ethane, propane, butane, and 2-methylpropane), assuming that the Level III EQC is used, these chemicals and those from other sources will not span the range of chemicals present in the 161 substances. This is particularly true for the higher molecular weight hydrocarbons and the inorganics present in many of the substances.

Biodegradation – The submitter suggests that, because the components chosen for testing (methane, ethane, propane, butane, 2-methylpropane, and sweetened LPG) are unlikely to be degraded by biological processes and “...available test methods are unsuitable for gases...”, the biodegradation component of the Test Plan will be fulfilled with a technical discussion. While a technical discussion may be adequate for these hydrocarbons in their pure state, when they are present as a component of a complex mixture (as is the case with most of the category) they may be present in soil and groundwater where biological processes may account for much of their removal from the environment. These components can serve as co-solvents that enhance the migration and retention in water and soil, so that considering the chemicals in the absence of the mixtures of which they are a component may lead to unsupportable conclusions.

Therefore, suggesting that biodegradation is unimportant on the basis of the physical and chemical properties of the pure components of the test substances or Level 1 EQC results may not adequately account for their true importance in the environment when they are present in a mixture. Additionally, the Level III EQC model suggests that some of the hydrocarbons may be present in water at concentrations much higher than those predicted by Level I. In the soil or water (particularly groundwater), biodegradation may be an important removal mechanism and the sponsor needs to consider how its significance could be determined experimentally for appropriate substances. In addition, the test plan indicates that no information will be generated for the components that are outside the range of test chemicals including the inorganic chemicals, which may significantly impact the environment.

Health Effects. EPA has the following specific comments on the proposed health test plan:

Excluding methane from the proposed testing. The sponsor’s argument that methane need not be tested because it is “known to be present at high concentrations in intestinal gases” is flawed. This does not exclude the possibility of potential effects from inhalation exposure to methane gas.

Proposed acute toxicity testing to assess central nervous system toxicity. The sponsor has submitted some acute toxicity data on some of the pure substances in its proposed category. The individual gases, where they have been tested, have been shown to be acutely toxic only at very high levels (>20% of the air available to the test animal). The proposal to test individual gases at high levels (one-half of the lower explosive limit) for potential central nervous system toxicity may not yield results that would enhance our understanding of these HPV chemicals.

Proposing different tests for the individual gases versus the sweetened LPG mixture. The sponsor plans to conduct 28-day repeat dose toxicity studies for ethane, propane, butane, and isobutane, but a 90-day study for sweetened LPG. The reason for the difference is not clearly presented. Similarly, the reason (“greatest likelihood of potential exposure to the population at large”) provided for proposing OECD 414 (developmental toxicity study) for the sweetened LPG mixture versus OECD 421 (combined reproductive toxicity/developmental toxicity study) for the individual gases is not sufficient to justify a different approach. Different tests with the mixture will not allow an appropriate comparison with the test results from the individual gas studies in terms of a category analysis.

Genotoxicity - Ames test for ethane. Although not proposed, it appears that the sponsor has not accounted for the gene mutation endpoint for ethane. Ethane was not one of the six gases included in the Ames test summarized in the submitted robust summary.

Reproductive toxicity endpoint - sweetened LPG mixture. The sponsor did not state how this SIDS endpoint would be satisfied for the sweetened LPG mixture.

Alternative toxicity test protocols. An alternative to the proposed testing scheme for the repeat dose, developmental, and reproductive toxicity endpoints would be to perform OECD 422 (combined repeat dose/reproductive/developmental toxicity test) studies on the four individual gases and the sweetened LPG mixture.

Environmental Effects.

The sponsor's plan to estimate these endpoints with the ECOSAR program is generally acceptable, but cannot be adequately evaluated without additional information on composition ranges of the category members, including the inorganics and mercaptans mentioned in the submission. Calculations or data for substances of carbon content >C5, inorganics and mercaptans need to be included as appropriate for the category.

Specific Comments on the Robust Summaries

Chemistry

The sponsor's robust summary treatment of the physicochemical endpoints for the Petroleum Gases category is acceptable.

Fate

The sponsor's robust summary treatment is acceptable.

Transport/Distribution

The sponsor estimated the fugacity of these chemicals using a Level I EQC model. Although EPA had previously recommended the use of EQC Level I, this model is somewhat limited. EPA now recommends the use of EQC level III, which provides a more rigorous level of analysis. EPA recommends using the EQC Level III model from the Canadian Environment Modeling Centre at Trent University. This model can be found at the following Web address:
<http://www.trentu.ca/academic/aminss/envmodel/>.

Health Effects

EPA evaluated six robust summaries (four for acute toxicity, one for repeated dose toxicity and one for genotoxicity) considered relevant to the U.S. HPV Challenge Program (the cardiac sensitization and irritation summaries are not reviewed here). All of the summaries were considered inadequate for the purposes of the HPV Challenge Program.

Following are EPA comments on the robust study summaries (the information identified as missing may be in the full study report):

Acute toxicity. The following information is missing from the propane and isobutane rat study summaries: (1) identification of each dose used in the experiment; (2) the post-exposure observation period; (3) number of dead animals per dose group; and (4) whether necropsy was performed and if so, the findings. Importantly, it appears from both summaries that the purity of the test compound was not specified.

The sponsor's assessment of two studies with butane (one with a rat and one with a mouse) as being invalid is reasonable.

Analysis: The propane and isobutane studies used an exposure duration of 15 minutes, which is short of the normal 4-hour exposure period used in acute inhalation toxicity experiments. However,

the information presented is useful in showing that extremely high levels are necessary for lethality (LC50's of >800,000 ppm and 570,000 ppm for propane and isobutane, respectively). These levels are equivalent to 80% and 57% of the air inhaled by the animal.

Repeat dose toxicity. This study was not an assessment of general repeat-dose toxicity but an experiment designed to assess the effects of the test substances on the rat kidney. Although, for the purposes of the U.S. HPV Challenge Program, the study is not acceptable to assess repeat dose toxicity, the information is still useful. However, the summary is missing the following information: (1) the nature and incidence of the nephrotoxic effect observed in the male rats after 20 exposures; and (2) the magnitude and incidence (by time point) of the decrease in body weights seen in males and females exposed to the n-butane/n-pentane mixture.

Genotoxicity The summary describes a study evaluating six alkane gases (propane, n-butane, two isobutane samples, n-pentane, and isopentane). The major concerns EPA has with this summary/study are the appropriateness of methylene chloride as a positive control for all *Salmonella* strains and the use of a six-hour exposure time. Evidence that methylene chloride is not a strong positive in all *Salmonella* strains comes from a study employing a 24-hour exposure period (Japan Chemical Industry Ecology-Technology & Information Center, [JETOC], 1997). The investigators found that methylene chloride was positive in strains TA98, TA100, and TA1535 (all both with and without activation, with response in TA1535 less than the other two strains), but not positive in TA1537.

In addition, the following information is missing from the summary: (1) criteria for a positive response (i.e., the background number of revertant colonies by strain); (2) the concentration of methylene chloride used as the positive control and whether any toxicity was associated with that concentration; (3) whether positive controls were used for strains TA1537 and TA1538; and (4) whether the observed toxicity at high concentrations for isopentane, n-pentane, and isobutane was equivalent across *Salmonella* strains.

Other comments: (1) it is unexplained which of the two isobutane test materials was toxic at a concentration of 50%; (2) ethane was not one of the gases tested and the sponsor does not plan to test for ethane; and (3) there is no documentation that six hours' exposure to the individual gases was sufficient.

Health Endpoints: Additional Information Available and not cited/used. EPA reviewed some of the sources cited in the submission and found additional sources in its own search. Additional information could be added to the submission by reviewing and including information from the following citations:

Aviado, et al. 1977. (Reference 5 in th submission). Although a review, this text presents original data onthe acute toxicity of isobutane (Chapter 6) and an acute toxicity experiment with a mixture of propane, butane, and isobutane (Chapter 7).

NTP Database.

http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html

Cosmetic Ingredient Review. 1982. Final Report of the Safety Assessment of Isobutane, Isopentane, n-Butane, and Propane. *J. Amer. Coll. Tox.* (1)(4): 127.

Dow Chemical, Undated. *Acute inhalation toxicity of aerosols from Scotchgard Fabric Protectors.* EPA Number OTS 0206660 (received by EPA in 1984).

Environmental Effects

A robust summary was submitted for one study addressing methane, propane, and butane.

EPA evaluated the robust summary and determined that it was inadequate; insufficient information was

presented, apparently reflecting the underlying study report.

Followup Activity

EPA requests that the Sponsor advise the Agency within 90 days of any modifications to its submission.