

Analysis of the High Production Volume Challenge: Industry Violations and EPA Negligence

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Executive Summary

The Environmental Protection Agency's (EPA's) High Production Volume (HPV) Challenge encourages chemical companies to volunteer to conduct screening-level animal toxicity tests on 2,800 industrial chemicals. Pursuant to this program, companies have committed to provide available toxicity information and present proposals to test chemicals. Researchers at the Physicians Committee for Responsible Medicine (PCRM) have reviewed all 24 HPV Challenge test plans submitted to the EPA as of August 1, 2001, evaluating each test plan for compliance with the original HPV Challenge framework as well as animal welfare guidelines issued by the EPA. This review found major and recurring flaws in the program's execution as well as its fundamental design. Of the 24 test plans submitted, 18 (75 percent) violate fundamental terms of the program. Many participating companies have failed to conduct comprehensive analyses of available data and have instead proposed unnecessary and inhumane tests. Furthermore, the program's exclusion of human health and exposure data is leading to irrelevant experiments that will not protect human health or the environment.

Introduction

In April 1998, former Vice President Al Gore announced the "Chemical Right-to-Know Program," a national initiative aimed at making hazard information about chemicals available to the public. In October of that year, the Environmental Protection Agency (EPA) announced, as part of this initiative, the High Production Volume (HPV) Challenge. This plan encourages chemical manufacturers, importers, and distributors to volunteer to conduct screening-level animal toxicity tests on 2,800 industrial chemicals produced or imported in the United States in amounts exceeding 1 million pounds per year.

The impetus for the HPV Challenge came from a July 1997 report entitled *Toxic Ignorance*, issued by the environmental group Environmental Defense and the April 1998 EPA report *Chemical Hazard Data Availability Study: What Do We Really Know About the Safety of High Production Volume Chemicals?* These papers suggested that basic information about many HPV chemicals is not available. In December 1998, PCRM conducted its own analysis, finding data in publicly available databases overlooked by Environmental Defense and the EPA that were sufficient for basic hazard assessments of the majority of the chemicals. This information is documented in PCRM's report entitled *Availability of HPV Chemical Data*.

During its design, the HPV Challenge was never subjected to scientific and public comment. Only later did a notice appear in the *Federal Register*, but no comments were solicited. PCRM president Dr. Neal Barnard testified before the House Subcommittee on Energy and the Environment in June 1999 and demonstrated that much of the data the EPA thought were lacking were, in fact, readily available. Dr. Barnard also pointed out that the list of chemicals slated for testing included chemicals with well-known toxicity, such as carbon tetrachloride, turpentine, tetraethyl lead, and cyclonite rat poison.

HPV Program Implementation

The HPV Challenge is a voluntary program, wherein chemical manufacturers, producers, and importers volunteer to submit testing proposals to the EPA for certain chemicals. The agency makes these test plans publicly available and allows comments from interested parties for 120 days thereafter. Under the program, participating companies are to provide all available information that would be relevant to the hazard characterization to avoid unnecessary or duplicative testing. More than 400 companies are not participating in the program, and in-house data from these non-participating companies is not being used in the program. The HPV Challenge ignores all human toxicity and exposure data.

The series of tests the EPA has requested under the HPV program is based on the Organization of Economic Cooperation and Development's (OECD's) Screening Information Data Set (SIDS), which calls for experiments in six areas: acute toxicity, repeat dose toxicity, developmental and reproductive toxicity, mutagenicity, ecotoxicity, and environmental fate. This test battery includes as many as seven animal tests and two *in vitro* tests. (See Appendix A.)

As a result of concerns raised by PCRM and other organizations, a compromise was reached among chemical manufacturers, the EPA, and environmental, health, and animal protection groups in October 1999. This October Agreement took the form of a guidance letter from the EPA to all HPV participants dated October 14, 1999, which delineated principles for minimizing irrelevant and repetitive tests and considering animal welfare provisions. The ten points of the agreement include, in part:

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 are 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 data and scientifically adequate data to minimize further testing.
3. Participants shall maximize the use of scientifically appropriate categories of related chemicals and structure activity relationships.
4. Consistent with the Screening Information Data Set (SIDS) program of the Organization for Economic Cooperation and Development (OECD), participants shall not conduct any terrestrial toxicity testing.
5. 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.
6. Consistent with the OECD/SIDS program, participants generally should not develop any new dermal toxicity data.
7. Participants shall not develop sub-chronic or reproductive toxicity data for the HPV chemicals that are solely closed system intermediates, as defined by the OECD/SIDS guidelines.

8. In analyzing the adequacy of screening data for chemicals that are substances Generally Recognized as Safe (GRAS) for a particular use by the Food and Drug Administration (FDA), participants should consider all relevant and available information supporting the FDA's conclusions. Participants reviewing the adequacy of existing data for these chemicals should specifically consider whether the information available makes it unnecessary to proceed with further testing involving animals. As with all chemicals, before generating new information, participants should further consider whether any additional information obtained would be useful or relevant.
9. Because validated non-animal tests for some SIDS endpoints may be available soon, participants shall make the following revisions to the sequence of testing:
 - (a) Testing of closed system intermediates, which present less risk of exposure, shall be deferred until 2003;
 - (b) Individual chemicals (i.e. those HPV chemicals not proposed for testing in a category) that require further testing on animals shall be deferred until November 2001.
10. Companies shall allow 120 days between the posting of tests plans and the implementation of any testing plans.

The EPA's Susan Wayland, Charles Auer, and Oscar Hernandez reiterated these principles in October 2000 in letters to all HPV participants and trade associations. The EPA further emphasized this guidance in the *Federal Register* Notice 65 Fed. Reg. 81686 (December 26, 2000) entitled *Data Collection and Development on High Production Volume (HPV) Chemicals*.

Research Methods

PCRM has evaluated each test plan that has been submitted to the EPA and subjected to public comment under the HPV Challenge program as of August 1, 2001, to evaluate compliance with the original HPV framework and the October Agreement. Specifically, PCRM has examined each test plan along the following parameters: adequate presentation of existing data, appropriate use of chemical categories, testing within the scope of the HPV program, and consideration of whether or not proposed experiments would advance the understanding of the test substances' potential health risks.

PCRM evaluations entailed searches of publicly available databases for relevant toxicity studies, analyses of physical and chemical properties, environmental fate and transport, human exposure assessments, and epidemiological studies. The databases searched include PubMed, Chemfinder, Toxline, Hazard Substances Database, the EPA's Integrated Risk Information System, and the National Toxicology Program study results database. Additionally, PCRM ascertained whether the sponsored chemicals were already regulated by other federal agencies, such as the Food and Drug Administration (FDA) or the Occupational Safety and Health Administration (OSHA). PCRM identified exposure limits recommended by these agencies as well as the National Institute for Occupational Safety and Health (NIOSH). PCRM also performed basic Internet searches and consulted toxicology textbooks.

After reviewing available information on these chemicals, PCRM researchers assessed whether or not the tests proposed by chemical companies would expand relevant knowledge of the risk posed by the chemicals to the environment or public health.

Results

Of the 24 test plans reviewed by the EPA as of July 26, 2001, 18 (75 percent) contained substantive violations. These violations are presented in Table 1 and Table 2. These problems recur with such sufficient frequency that they cast serious doubt on the participants' ability to carry the program through and the EPA's commitment to properly administering the program. Most notably:

1. Chemical manufacturers have repeatedly failed to report existing hazard information.
2. Opportunities to group structurally or toxicologically similar chemicals are not being utilized.
3. Many companies are proposing animal tests beyond the scope of the HPV program.
4. The EPA is not enforcing the original HPV framework or the principles outlined in the October Agreement.

In addition, implementation of the program to date shows these major flaws in the program's fundamental design:

5. The HPV program excludes exposure and use information that would make hazard information meaningful.
6. The HPV program is focused exclusively on nonhuman data, even though human toxicity, exposure, and epidemiological studies have been performed on many of the sponsored chemicals.
7. Available *in vitro* tests using aquatic microorganisms are being neglected.

These problems of the HPV Challenge program are discussed below:

1. Chemical manufacturers have repeatedly failed to report existing hazard information.

Under the HPV program, chemical companies have committed to conducting comprehensive literature reviews of existing data to determine if any further animal tests should be conducted. This idea was reiterated in the October Agreement, which states that "participants shall conduct a thoughtful, qualitative analysis rather than use a checklist approach...Participants shall maximize the use of existing and scientifically adequate data to minimize further testing."

Of the 24 test plans that underwent the 120-day public review as of August 1, 2001, 15 called for new testing. Of these, PCRM found additional available hazard information that had been overlooked or otherwise omitted for 8 of the 15 (53 percent) chemicals. (See Table 1, Table 2.) Because companies have, in these instances, not been thorough in their review of existing data, many studies will be unnecessarily duplicated. In many cases, the available information on the toxicity and metabolism of chemicals far surpassed the basic information that can be ascertained by the SIDS battery.

For example, the American Petroleum Institute (API) proposed a series of animal tests on petroleum coke, a solid, nearly pure carbon product resulting from petroleum processing and refining. In its test plan, the API failed to provide a complete review of data on the known health and environmental effects of these substances. Numerous toxicological studies have been conducted on animals. Additionally, epidemiological studies of petroleum workers exposed to petroleum coke and other related substances from petroleum coker facilities, carbon black operations, and coal coke dust document known human health effects.

The API also failed to present available information in its test plan for petroleum gases. Petroleum gases are products from natural gas processing and petroleum refining operations, and include chemicals such as methane, ethane, propane, and butane. At high doses, they displace oxygen. However, extensive human and nonhuman animal data already indicate that these compounds are relatively non-toxic. Moreover, people are generally exposed to very low doses. Illustrative of the generally benign chemical nature of these compounds is the fact that propane, n-butane, and isobutane are all classified as Generally Recognized as Safe (GRAS) for appropriate uses in food products by the Food and Drug Administration. The American Gas Association specifically requested that these compounds be exempt from the HPV program in a letter to the EPA, as these naturally occurring substances are already sufficiently well characterized and present a very low health risk. In defense of the HPV program, Dr. William Sanders, director of the EPA Office of Pollution Prevention and Toxics, testified before the U.S. House Science Subcommittee on Energy and the Environment in June 1999 that the EPA was “not requiring testing on butane.” Nevertheless, the API has proposed an unnecessary test series on ethane, propane, butane, and isobutane that will not contribute to the understanding of the sponsored substances’ toxicological characteristics, and the EPA failed to reject this excessive and inappropriate test plan.

In yet another example of inappropriate testing, the American Chemistry Council (ACC) proposed re-testing mixtures containing butadiene and isoprene, both of which are potential human carcinogens. Butadiene is a synthetic chemical used primarily in the production of rubber and plastics, and is also present in gasoline. The effects of butadiene chemicals have already been evaluated in humans in numerous occupational studies. These chemicals are known to be sufficiently dangerous. As such, screening-level animal tests are clearly unnecessary.

Exposure to the synthetic form of isoprene occurs in the manufacturing of rubber. Isoprene also occurs naturally in the environment as emissions from vegetation. The crude, screening-level tests proposed in this test plan will provide no insight that would facilitate the regulation of isoprene in the workplace. Extensive toxicological work is already being conducted on the kinetics of isoprene, and human metabolism, toxicological mechanisms, human biomarkers, and human physiologically based pharmacokinetic (PBPK) models should be further investigated. There is no appropriate role for the HPV test series in further evaluation of this chemical.

General Electric (GE) Plastics submitted three test plans for individual chemicals without providing even minimal information about the structure and use of the compounds. For example, in its test plan for tris(nonylphenol)phosphite (TNPP), GE failed to provide such basic information as the structure and use of the chemical, its physical properties, or the test method for each health endpoint. Additionally, the test plan disregarded the environmental fate and transport of the compound. Existing data on food products indicate that foods in contact with TNPP additives may contain levels of free nonylphenol, a product of a hydrolysis reaction of TNPP. Nonylphenol is a potential endocrine disruptor for which an abundance of data exists on its toxicological and physicochemical properties. Since nonylphenol may well be

the environmentally relevant moiety, a critical review of its properties and behavior is essential for a thorough analysis of the potential health effects of TNPP. However, application of the crude SIDS battery will not advance our understanding of the health risks in any meaningful way.

2. Opportunities to group structurally or toxicologically similar chemicals are not being utilized.

The October Agreement states, “Individual chemicals (i.e. those chemicals not proposed for testing in a category) that require testing on animals shall be deferred until November 2001.” However, 5 of the 15 (33 percent) test plans calling for animal tests were for individual chemicals, in clear violation of the October Agreement. (See Table 1, Table 2.) The failure to form chemical categories and apply structure activity relationships will result in repetitive and inefficient testing. For example, the individual chemicals submitted by GE could be grouped with other compounds. TNPP could be assessed in the context of a larger group of phenyl-phosphorous antioxidant stabilizers. p-Cumylphenol could be included in a larger substituted or alkylphenol category. In addition to reducing the costs and numbers of animals used in screening evaluations, formation of chemical categories provides a contextual basis to evaluate toxicity, providing a deeper understanding about compounds’ toxicity.

In another example, the API failed to coordinate with other chemical companies to include all related compounds in its analysis of petroleum coke. The composition of petroleum coke is very similar to other HPV chemicals, such as “coal, anthracite, calcined CAS #68187597” and coke, (coal) CAS #65996772, which were not included in this group. Using information about these other compounds would support a more in-depth analysis of the potential hazard of petroleum coke.

The API’s test plan for petroleum gases represents a missed opportunity to apply structure activity relationships to evaluate chemical toxicity. Petroleum gases include substances such as methane (natural gas), ethane, butane, isobutane, and propane. These gases are simple organic compounds with a simple progression of structures and identical functional groups throughout, meeting all criteria for application of structure activity relationships as outlined in EPA guidance. Yet, the EPA refused to support the category construction and the opportunity to use existing data that would both reduce animal use and overall cost.

In contrast, the test plans submitted by the Flavor and Fragrance High Production Volume Consortia represent thoughtful analyses of well-studied chemicals that have been used in structure activity relationships for many years. The Consortia demonstrated a good understanding about toxicokinetics of these compounds, many of which are classified as GRAS food ingredients by the FDA. Given that these compounds have been consumed by millions of people over many years, the resultant effects, if any, are available from human observation without the need to extrapolate from rodents. Regrettably, in the face of all the evidence presented, the EPA still is not convinced the category is reasonable.

3. Many companies are proposing animal tests beyond the scope of the HPV program.

The October Agreement states, “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.” However, 6 of the 24 test plans (25 percent) propose to use less sensitive genetic toxicity tests on animals

without justification. (See Table 1, Table 2.)

The October Agreement also states, “Consistent with the OECD/SIDS program, participants generally should not develop any new dermal toxicity data.” Yet, four test plans (17 percent) called for these lethal dermal dose tests. (See Table 1, Table 2.)

Although terrestrial toxicity testing is specifically proscribed, the API’s test plan for petroleum coke called for this test. (See Table 1, Table 2.)

Some test plans have offered no rationale for testing at all. GE Plastics submitted test plans for three individual chemicals that were mere checklists, with no rationale for conducting experiments and little information about its sponsored chemicals. GE proposed *in vivo* genotoxicity studies and dermal toxicity tests, in violation of the agreement.

The FMC Corporation submitted test plans for two individual chemicals, methallyl chloride (MAC) and 2,3-dihydro-2,2-dimethyl-7-benzofuranol (7OH). The test plan for 7OH called for acute dermal and *in vivo* genetic toxicity tests. The FMC Corporation volunteered these chemicals on March 10, 1999, yet did not submit test plans until February 13, 2001, *after the majority of the tests had been completed*. This company side-stepped the public review process and violated the October Agreement as well as the original framework that the HPV participants agreed to follow, both of which called for a comment period between the submitting of proposed test plans and their implementation.

4. The EPA is not enforcing the original HPV framework or the principles outlined in the October Agreement.

Despite its stated commitments to minimizing irrelevant tests, the EPA continues to make it difficult for companies to reduce testing and has endorsed rote checklist test plans from companies that propose testing beyond the scope of the HPV program.

According to the October Agreement, “[I]n analyzing the adequacy of screening data for chemicals that are food substances Generally Recognized as Safe (GRAS) for a particular use by the Food and Drug Administration (FDA), participants should consider all relevant and available information” and should specifically “consider whether the information available makes it unnecessary to proceed with further testing involving animals.” Yet, the EPA has supported the Flavor and Fragrance High Production Consortia’s proposals to unnecessarily dose fish with GRAS food ingredients, including components of cinnamon oil and terpenoid alcohols naturally occurring in fruits and vegetables.

The EPA deemed the aforementioned GE test plans that represented violations of the October Agreement to be “minimally acceptable” and pointed out some of the problems. It then failed to follow up on the matter.

The EPA did point out some of the violations in the FMC test plan in a letter to the company signed by Oscar Hernandez dated March 7, 2001, in which the EPA requested specifically that “FMC consider these concerns and advise the Agency within 30 days of any modifications to its submission.” However, the EPA did not follow up with the company directly, but simply reiterated concerns about violations in comments on its Web site on June 14, 2001. Only after PCR/M intervened did the company agree to drop some tests.

The American Forest and Paper Association (AF&PA) HPV Work Group submitted a test plan for spent pulping liquor, a highly alkaline, corrosive mixture that causes tissue damage immediately upon contact. Human or ecological exposures to these substances are highly unlikely, as the material remains on the manufacturing site and has limited commercial use. The AF&PA did not propose any mammalian tests with caustic substances, citing OECD documents clearly stating that any testing on animals that would cause pain and suffering and need not be carried out. However, the AF&PA did propose tests on fish with a neutralized mixture, despite the fact that the mixture's fundamental toxic property is lost after neutralization. Any tests with neutralized spent pulping liquor will produce meaningless results. A comment from the AF&PA's test plan essentially acknowledges these problems and that testing is being conducted simply to be a "team player":

"It will be necessary to neutralize the test material in order to bring it to a pH that is compatible with survival of the test organisms in order to perform the testing. This will affect the composition of the material and the results therefore may not represent the original substance. However, AF&PA will undertake the testing in the spirit of the HPV program."

The EPA did not reject this test plan. The EPA also accepted the API's test plan on petroleum gases, which included a series of tests on ethane, propane, butane, and isobutane, despite the fact that, as noted above, Dr. William Sanders testified before the U.S. House Science Subcommittee on Energy and the Environment in June 1999 that the EPA was "not requiring testing on butane."

The above points show the HPV Challenge participants are openly and frequently violating the program guidelines and the October Agreement. The EPA has ignored their violations, allowing excessive and inappropriate testing to proceed.

A review of the 24 test pans shows fundamental flaws in the HPV Challenge design. These problems are discussed below:

5. The HPV program excludes exposure and use information that would make hazard information meaningful.

The underlying assumption of the HPV program is that substances produced in large quantities automatically lead to high exposures and therefore threaten public health. The EPA states in the *Federal Register* Notice 65 Fed. Reg. 81686 (December 26, 2000) that "it is generally accepted that chemicals having a high level of production have an increased potential for exposure," but does not provide any support for this assumption. Typically, it has not proven true.

The aminosilanes, sponsored by the Silicones Environmental Health and Safety Council, break down immediately when released into the environment and therefore do not present a hazard. Yet, repeat dose and reproductive toxicity tests are being run for physically irrelevant endpoints. The petroleum gases are found in ambient and occupational environments at levels that are orders of magnitude below exposure limits.

The Flavor and Fragrance High Production Volume Consortia's test plans for terpenoid tertiary and primary alcohols underscore this fundamental flaw of the HPV program. The ingestion of the natural form of the terpenoid tertiary and primary alcohols in fruits and vegetables is more than an order of

magnitude greater than the ingestion of the manufactured form of these substances used as food flavoring additives. These HPV chemicals have been studied and classified as GRAS food ingredients by the FDA, showing that chemicals produced in large quantities are not necessarily harmful.

The EPA is asking for tests with the cinnamyl derivatives and the terpenoid tertiary and primary alcohols. These chemical categories, proposed by the Flavor and Fragrance High Production Volume Consortia, include common household substances found in fragrance and food flavoring products. These tests are difficult to justify.

The EPA approved the American Forest and Paper Association HPV Work Group's test plan for spent pulping liquor, a highly alkaline, corrosive mixture that causes tissue damage immediately upon contact. As noted above, human or ecological exposures to these substances are highly unlikely, as the material remains on the manufacturing site and has limited commercial use. The hazards associated with this mixture are already well-known and any information resulting from the SIDS battery would not change the understanding or handling of these corrosive chemicals.

Exposure information could be used to prioritize the 2,800 HPV chemicals so that companies are not wasting resources on studying naturally occurring substances and food additives, or chemicals that are present at undetectable levels in the environment.

6. The HPV program is focused exclusively on nonhuman data, even though human toxicity, exposure, and epidemiological studies have been performed on many of the sponsored chemicals.

The HPV Challenge program neglects human data that are already available and are most relevant for predicting human toxicity. In fact, many of the chemicals, such as butadiene, butane, spent pulping liquor, and others are already monitored or controlled in the occupational environment. Existing occupational studies of miners and refinery workers would provide relevant information for the API's petroleum coke test plan. The ACC's characterization of 1,3-butadiene is incomplete without summaries of the available human exposure, biomarker, and epidemiological studies. The API's petroleum gas plan calls for testing on animals with common substances, such as propane, butane, methane, and ethane, which come from natural gas processing and petroleum refining operations. By the API's own admission, extensive human and nonhuman animal data already indicate that these compounds are relatively non-toxic.

The neglect of human data presents major problems for interpretation. Results from animal experiments must be extrapolated from high to low doses, and then from rats and mice to humans. The uncertainties involved in these assumptions reduce the validity and accuracy of risk assessments. For example, significant intra- and interspecies differences in effects of butadiene and isoprene have hindered the understanding of the behavior of these potential carcinogens in humans. This failure to incorporate existing human health data is currently impeding reassessment and regulatory action by the EPA.

7. Available *in vitro* tests using aquatic microorganisms are being neglected.

Protozoan members of Ciliophora, such as the Tetrahymena, are frequently used as a measure of aquatic toxicity in ecological risk assessments (Larsen et al, 1997). The biochemistry and physiology of Tet-

rahymena have been thoroughly investigated since the 1950s, and Tetrahymena, especially *T. pyriformis*, have been used for aquatic toxicity testing since the 1970s. Moreover, the genomics of the organism are currently being elucidated. The *T. pyriformis* population growth test is quick, easy, and inexpensive, and has considerable breadth (Schultz, 1997). It allows the examination of a large number of independent organisms that possess features of both single eukaryotic cells and multicellular organisms. Studies at varying concentration levels can easily be repeated, and many chemicals can be examined in a short period of time. Range-finding tests allow accurate approximation of both the highest concentration with no observed effect on population growth and the lowest concentration with total inhibition of cell replication. Fish toxicity tests are less economical, less humane, slower, and more labor intensive.

The EPA has a massive database on the acute toxicity of more than 600 organic chemicals to fish called “Acute Toxicities of Organic Pollutants to Fathead Minnows (*Pimephales promelas*).” Comparisons of toxicity test results from the *in vitro* TETRATOX assay and the EPA’s fish acute toxicity data have yielded good correlation between the two methods (Sinks et al, 2001). Similarly, good correlation was observed between ciliate and guppy fish toxicity (Seward et al, 2001). Moreover, where there is not good agreement, there is a logical rationale for this departure (Bearden and Schultz, 1998). Evaluation of *in vitro* and *in vivo* aquatic toxicity data has allowed researchers to develop models to predict toxicity based on quantitative structure activity relationships (QSARs) (Schultz, 1999; Schultz and Cronin, 1999; Niculescu et al, 2000). Both the *in vitro* TETRATOX assay as well as QSARs provide more humane, efficient methods to predict aquatic toxicity at the screening level.

Unfortunately, there is no mechanism in the HPV program for eliminating testing on fish based on the physical properties of the chemical. Therefore, substances with low observed toxicity or compounds with low water solubility, such as the cinnamon oil components, have been proposed for unnecessary testing on fish. Highly volatile compounds, such as the petroleum gases, are unlikely to pose a hazard to fish, yet the API proposed *in vivo* aquatic toxicity tests.

Conclusion

As of August 1, 2001, 24 test plans have been submitted to the EPA and undergone the full public comment period under the HPV Challenge program. PCR/M has submitted comments on nearly all test plans, yet the EPA has failed to respond to even one set of comments. Despite clear-cut guidelines for the conduct of this program, many participating companies have provided test plans that fail to bring forth relevant data and have instead proposed unnecessary, expensive, and inhumane tests. Furthermore, the program’s exclusion of existing human health and exposure data is leading to duplicative and irrelevant tests that will not protect public health or the environment.

The program is estimated to cost the EPA \$16 million each year to administer. EPA officials have expressed concern about their ability to handle the deluge of incoming data and they have been unable to appropriately follow up on the 24 test plans to date. They have provided mixed messages to companies by repeatedly expressing a commitment to reducing irrelevant tests, but then requesting unnecessary animal tests for substances with low toxicity, such as cinnamon oil and ethane. EPA officials have requested additional tests on potential carcinogens instead of recommending regulatory action. They have asked for tests on neutralized solutions of corrosive substances, when the hazards of the toxic compounds are well understood and tightly controlled. In other words, the EPA has insisted—contrary to the October Agreement and good science—that companies “check the box” rather than perform a thoughtful, useful analyses. The EPA’s presumption is that more animal testing is usually required and that

obstacles continue to be raised for those companies that attempt to use categories, structure activity relationships, or existing data.

Experience to date with the HPV Challenge indicates it is poorly administered and haphazardly conducted, and will do nothing to protect human health or the environment.

References

- Bearden AP, Schultz TW. Comparison of *Tetrahymena* and *Pimephales* toxicity based on mechanism of action. SAR QSAR in Environmental Research 1998;9:127-53.
- Dimitrov SD, Mekenyan OG, Schultz TW. Interspecies modeling of narcotics toxicity to aquatic animals. Bulletin of Environmental Contamination and Toxicology 2000;65:399-406.
- Niculescu SP, Kaiser LE, Schultz TW. Modeling the toxicity of chemicals to *Tetrahymena pyriformis* using molecular fragment descriptors and probabilistic neural networks. Archives of Environmental Contamination and Toxicology 2000;39:289-98.
- Schultz TW. Tetratox: *Tetrahymena pyriformis* population growth impairment endpoint—a surrogate for fish lethality. Toxicological Methods 1997;7:289-309.
- Schultz TW. Structure-toxicity relationships for benzenes evaluated with *Tetrahymena pyriformis*. Chemical Research in Toxicology 1999;12:1262-7.
- Schultz TW, Cronin MTD. Response-surface analyses for toxicity to *Tetrahymena pyriformis*: reactive carbonyl-containing aliphatic chemicals. Journal of Chemical Information and Computer Sciences 1999;39:304-9.
- Seward JR, Hamblen EL, Schultz TW. Regression comparison of *Tetrahymena pyriformis* and *Poecilia reticulata* toxicity. Chemosphere 2001;(in press).
- Sinks GD, Schultz TW. Correlations of *Tetrahymena* and *Pimephales* toxicity: evaluation of 100 additional compounds. Environmental Toxicology and Chemistry 2001;20:917-21.

Table 1: Violations of the High Production Volume Challenge's October Agreement

Violation of October Agreement	Test Plans Violating the Guideline*	Test Plans Violating the Guideline*
		* Percentage out of 24 submitted test plans.
Failure to conduct a thorough analysis and consider whether or not further testing is needed (Guideline #1)	14 (58%)	petroleum coke; aminosilanes; high butadiene C4; phosphorus acid, cyclic neopentantetracyl diphenyl ester; p-cumylphenol; tris(nonylphenol)phosphite; tetrakis-(methylene-3,5-ditertbutyl-4-hydroxycinnamate)methane; octadecyl 3,5-di(tert)butyl-4-hydroxyhydrocinnamate; tris(2,4-di(tert)-butylphenyl)phosphite; petroleum gas; C5 noncyclics; methallyl chloride; 2,3-dihydro-2,2-dimethyl-7-benzofuranol; spent pulping liquor and cooking liquors
Failure to Incorporate Existing Data (Guideline #2)	13 (54%)	petroleum coke; high butadiene C4; p-cumylphenol; tris(nonylphenol) phosphite; tetrakis-(methylene-3,5-ditertbutyl-4-hydroxycinnamate)methane; octadecyl 3,5-di(tert)butyl-4-hydroxyhydrocinnamate; tris(2,4-di(tert)-butylphenyl)phosphite; petroleum gas; C5 noncyclics; aminosilanes; cinnamyl derivatives; terpenoid tertiary alcohols and related esters; terpenoid primary alcohols and related esters
Failure to Appropriately Use Categories (Guideline #3)	8 (33%)	petroleum coke; phosphorus acid, cyclic neopentantetracyl diphenyl ester; tris(nonylphenol)phosphite; tetrakis-methylene-(3,5-ditertbutyl-4-hydroxycinnamate) methane; octadecyl 3,5-di(tert)butyl-4-hydroxyhydrocinnamate; tris(2,4-di-(tert)-butylphenyl)phosphite; petroleum gas; C5 noncyclics
Proposal of Terrestrial Toxicity Testing (Guideline #4)	1 (4%)	petroleum coke
Proposal of In Vivo Genotoxicity Tests without Justification (Guideline #5)	6 (25%)	cyclic neopentantetracyl diphenyl ester phosphorus acid; p-cumylphenol; tris(nonylphenol) phosphite; petroleum gas; C5 noncyclics; 2,3-dihydro-2,2-dimethyl-7-benzofuranol
Proposal for Dermal Toxicity Tests (Guideline #6)	4 (17%)	cyclic neopentantetracyl diphenyl ester phosphorus acid; p-cumylphenol; tris(nonylphenol) phosphite; 2,3-dihydro-2,2-dimethyl-7-benzofuranol
Proposal of Inappropriate Tests Closed System Intermediates (Guideline #7 and #9a)	0 (0%)	none
Failure to Consider Whether Tests Would Provide Useful or Relevant Information, Including GRAS Chemicals (Guideline #8)	10 (42%)	petroleum coke; aminosilanes; high butadiene C4; cyclic neopentantetracyl diphenyl ester phosphorus acid; p-cumylphenol; tris(nonylphenol) phosphite; petroleum gas; cinnamyl derivatives; terpenoid tertiary alcohols and related esters; terpenoid primary alcohols and related esters
Proposal to Conduct Animal Tests with Individual Chemicals (Guideline #9b)	5 (21%)	cyclic neopentantetracyl diphenyl ester phosphorus acid; p-cumylphenol; tris(nonylphenol) phosphite; methallyl chloride; 2,3-dihydro-2,2-dimethyl-7-benzofuranol
Any Guideline of the October Agreement	18 (75%)	petroleum coke; aminosilanes; high butadiene C4; cyclic neopentantetracyl diphenyl ester phosphorus acid; p-cumylphenol; tris(nonylphenol) phosphite; tetrakis-(methylene-3,5-ditertbutyl-4-hydroxycinnamate)methane; octadecyl 3,5-di(tert)butyl-4-hydroxyhydrocinnamate; tris(2,4-di(tert)-butylphenyl)phosphite; petroleum gas; C5 noncyclics; methallyl chloride; 2,3-dihydro-2,2-dimethyl-7-benzofuranol; spent pulping liquors and cooking liquors; cinnamyl derivatives; terpenoid tertiary alcohols and related esters; terpenoid primary alcohols and related esters

Table 2: High Production Volume Program Violations

Date Posted	Company	Chemical	October Agreement Guideline Violated*
04/21/00	American Petroleum Institute	petroleum coke	1,2,3,4,8
04/21/00	Silicones Environmental Health and Safety Council	aminosilanes	1,8
05/19/00	American Chemistry Council Olefins Panel	high butadiene C4	1,2,8
06/13/00	American Chemistry Council Health, Environmental, and Regulatory Task Group (HERTG)	alkyl sulfide category	2
06/13/00	GE Plastics	phosphorus acid, cyclic neopentatetrayl diphenyl ester	1,3,5,6,8,9b
06/13/00	GE Plastics	p-cumylphenol	1,2,5,6,8,9b
06/13/00	Phosphite Producers HPV Consortium	tris(nonylphenol) Phosphite	1,2,3,5,6,8,9b
07/20/00	Ciba Specialty Chemicals-Additives	tetrakis-(methylene-(3,5-ditertbutyl-4-hydrocinnamate)methane	1, 2, 3
07/20/00	Ciba Specialty Chemicals-Additives	octadecyl 3,5-di(tert)-butyl-4-hydroxyhydrocinnamate	1, 2, 3
07/20/00	Ciba Specialty Chemicals-Additives	tris(2,4-di-(tert)-butylphenyl)phosphite	1, 2, 3
08/03/00	Silicones Environmental, Health, and Safety Council	silane [3-(2,3-epoxypropoxy)propyl]trimethoxy	none
09/05/00	The Lubrizol Corporation	AMPS	none
09/11/00	American Petroleum Institute	petroleum gas	1,2,3,5,8
11/20/00	DuPont SHE Excellence Center	dimethyl ether	none
12/01/00	American Chemistry Council	C5 noncyclics	1,2,3,4,5
12/19/00	The Dioxolane Manufacturers' Consortium	1,3-dioxolane	none
01/12/01	The HPV Trioxane Manufacturers' Consortium	1,3,5-trioxane	none
02/07/01	The Flavor and Fragrance High Production Volume Consortia	cinnamyl derivatives	8
02/07/01	Exxon Mobil Chemical Corporation	alkyl acetate C6-C13 category	none
02/13/01	FMC Corporation	methallyl chloride	1,5,6,9b,10
02/13/01	FMC Corporation	2,3-dihydro-2,2-dimehtyl-7-benzofuranol	1,5,6,9b,10
02/14/01	The Flavor and Fragrance High Production Volume Consortia	terpenoid tertiary alcohols and related esters	8
02/20/01	The American Forest and Paper Association HPV Work Group	spent pulping liquor and cooking liquors	1
03/20/01	The Flavor and Fragrance High Production Volume Consortia	terpenoid primary alcohols and related esters	8

* See Appendix B for outline of October Agreement Guidelines.

Appendix A: The HPV Animal Test Battery

Acute Toxicity

Acute toxicity is traditionally evaluated with the Lethal Dose test, or LD50. This Lethal Dose test involves the administration of a substance to a group of animals at increasing doses in order to determine the dose that kills 50 percent of the tested animals within a set time frame. Typically, administration of the test substance is via a tube inserted down the esophagus into the stomach. Other routes of administration include inhalation and applying the substance to the animals' skin (the dermal toxicity test). The test is typically allowed to proceed for 14 days, at which time all the animals who have not died from the test substance are killed. When experimenters are interested in studying dermal toxicity, they shave the fur on the animals' backs and then apply the chemical. The dose is increased until 50 percent of the animals die from the application of the chemical on their skin. All the animals are then killed and dissected.

Genetic Toxicity

In vitro tests are used in which bacteria or cell cultures are treated with the chemical and observed for mutations in the DNA or abnormality in the chromosomes. Animal tests are also used, such as the *in vivo* mammalian erythrocyte Micronucleus Test, in which the chemical is typically injected into the animals' stomachs. The animals are then killed, and their bone marrow is extracted and examined for abnormalities indicative of a structural or numerical chromosomal aberrations.

Repeat Dose Toxicity

The typical test used is the repeated dose 28-day oral toxicity screening test, in which the chemical is force-fed to young animals through a stomach tube in incremental doses over a period of 28 days. Once a week, the animals are checked for weight loss, changes in eating habits, abnormal behavior, and death. At least 40 animals are used in this test per chemical.

Reproductive and Developmental Toxicity

Male and female rats and mice are dosed with the chemical and then mated. Problems in reproductive function and fertility are observed. The test provides that 20 pregnant female rats be brought to term. After the animals give birth, they are killed and dissected, with special attention to their reproductive organs. Birth defects in the offspring are noted.

Acute Toxicity to Fish

Fish are exposed to various concentrations of a chemical for four days. At the end of each 24-hour period, the experimenters count how many fish have died. At least 42 fish are killed for each chemical tested. The goal of the test is to estimate the LC50, or lethal concentration 50, the concentration of chemical that kills half the fish.

Appendix B: The HPV October Agreement

October 14, 1999

Company name

Street

City, State, Zip

Dear Company Contact:

On behalf of the Environmental Protection Agency (EPA), I would like to thank you for your commitment to participate in the voluntary High Production Volume Challenge (HPV) program. We look forward to working with you over the coming years as we achieve our goals for this important program.

As you may be aware, a number of animal protection organizations and the public have raised concerns that the HPV Challenge program may lead to the excessive use of animals in tests and to inadequate attention to existing information and alternative testing methods that do not require animals as test subjects. As a general matter, animal experiments should not be performed if another validated method—not involving the use of animals—is reasonably and practically available for use in the HPV Challenge program. To respond to these concerns, and after consultation with the organizations involved in developing the framework for this initiative, I am asking you and your fellow HPV Challenge participants to observe the following principles as we proceed with the program:

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. To reinforce this approach, EPA will consider information contained in the databases identified in the enclosure, or in databases maintained by the organizations identified in the enclosure, to have been known to the Agency within the meaning of Section 8(e) of the Toxic Substances Control Act (TSCA), 42 U.S.C. 2607(e). This policy is limited to information reported by participants under the HPV Challenge program and generated for or contained in these databases as of the date of this letter. In addition, any other potential liability under TSCA Section 8(e) for existing data on HPV Challenge program chemicals will be limited according to the terms of the “Registration Agreement for TSCA Section 8(e) Compliance Audit Program (56 Fed. Reg. 4128, Feb. 1, 1991).” This policy does not affect prior 8(e) enforcement actions.
3. Participants shall maximize the use of scientifically appropriate categories of related chemicals and structure activity relationships.
4. Consistent with the Screening Information Data Set (SIDS) program of the Organization for Economic Cooperation and Development (OECD), participants shall not conduct any terrestrial toxicity testing.
5. 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.
6. Consistent with the OECD/SIDS program, participants generally should not develop any new dermal toxicity data.
7. Participants shall not develop sub-chronic or reproductive toxicity data for the HPV chemicals

that are solely closed system intermediates, as defined by the OECD/SIDS guidelines.

8. In analyzing the adequacy of screening data for chemicals that are substances Generally Recognized as Safe (GRAS) for a particular use by the Food and Drug Administration (FDA), participants should consider all relevant and available information supporting the FDA's conclusions. Participants reviewing the adequacy of existing data for these chemicals should specifically consider whether the information available makes it unnecessary to proceed with further testing involving animals. As with all chemicals, before generating new information, participants should further consider whether any additional information obtained would be useful or relevant.
9. Because validated non-animal tests for some SIDS endpoints may be available soon, participants shall make the following revisions to the sequence of testing:
 - (a) Testing of closed system intermediates, which present less risk of exposure, shall be deferred until 2003;
 - (b) Individual chemicals (i.e., those HPV chemicals not proposed for testing in a category) that require further testing on animals shall be deferred until November 2001.These revisions should not be construed to suggest that delay or deferral is appropriate with respect to testing of scientifically appropriate categories of related chemicals.
10. Companies shall allow 120 days between the posting of test plans and the implementation of any testing plans.

To promote the availability and use of alternatives to tests involving animals, the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP) will commit at least \$1.5 million in FY 2000, and \$3 Million in FY 2001, and any further funds appropriated by Congress, to the development and validation of non-animal alternative test methods and protocols. EPA will provide an additional \$250,000 this year and will seek to provide a similar amount next year to these efforts. The Multicenter Evaluation of In Vitro Cytotoxicity (MEIC), on the agenda for the October 14 meeting of NTP's Advisory Committee on Alternative Toxicological Methods, will be given priority attention. EPA will promptly incorporate, as appropriate, the work of NIEHS and NTP into the HPV Challenge program.

EPA recognizes that the HPV Challenge is a voluntary program that includes substantial public review and involvement. The successful implementation of the changes described in this letter will depend upon the good faith effort and cooperation of all parties. We appreciate the spirit of cooperation and commitment that has characterized this initiative to date. The changes to the HPV Challenge program outlined above present the opportunity to advance our shared goals of expanding the basic health data available to the public, while incorporating certain animal welfare concerns and scientific principles. It is the intention of the Agency that the HPV Challenge program, including the test rule(s), should proceed in a manner that is consistent with these principles and concerns.

Again, I thank you for your commitment to participate in the HPV Challenge program. If you need further clarification or assistance with this program, please contact Barbara Leczynski at 202-260-3749 or visit the website at www.epa.gov/chemrtk.

Sincerely,

/s/

Susan H. Wayland
Deputy Assistant Administrator