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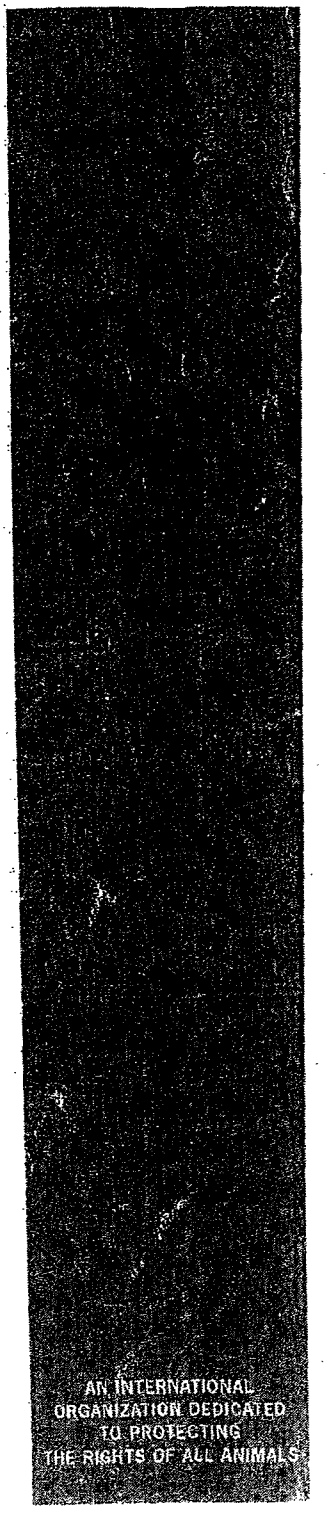

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Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, DC 20460

RE: DOCKET CONTROL #OPPTS-42213A

These comments on the Environmental Protection Agency's (EPA's) *Federal Register* notice of 12-26-2000, entitled "Testing of Certain High Production Volume Chemicals," are submitted on behalf of People for the Ethical Treatment of Animals (PETA) and Earth Island Institute (EEI). PETA is the world's largest animal rights organization with 700,000 members who are concerned about the suffering of animals used in laboratory experiments. EEI is an environmental protection organization with 100,000 members. In addition to submitting these comments, we support the comments submitted by the Physicians Committee for Responsible Medicine (PCRM).

These comments on the proposed rule are based in part on the experience our organizations have had with the EPA's high production volume (HPV) "voluntary Challenge" program. PETA and several other animal protection organizations have been the *only* stakeholders to comment consistently on every test plan submitted by industry under the HPV Challenge Program (see comments on test plans posted through December 2000 at http://www.epa.gov/chemrtk/viewsrch.htm). PETA's involvement with the "voluntary" HPV program dates back to November 1998 when we learned of the implementation of this massive animal-testing program.

As a general matter, PETA is concerned that the December 26, 2001, *Federal Register* notice represents the first time a program of this magnitude, that was implemented more than two years ago, has been noticed in the *Federal Register*. This *Federal Register* notice of both the test rule and the "voluntary" program is an extremely belated attempt to address what has been a glaring lack of public notice and participation to date. Because the HPV Challenge Program was developed behind closed doors by the EPA, the Environmental Defense Fund (EDF), and the Chemical Manufacturers Association (CMA), the public was never afforded notice or an opportunity to comment on the program prior to its implementation.

The EPA states in section IIID(1) that the "voluntary" program "was created with industry, environmental groups, and other interested parties." To the best of our knowledge there were no other "interested parties" involved. Hence, the largest animal rights organization in the world was unaware of the largest animal-testing program ever proposed to date until after the program's

structure was well established. As a result, the HPV Challenge Program failed to include even minimal animal protection concerns and did not receive the benefit of scientific peer review. The flaws inherent in a program that circumvents such review are apparent in the test plans submitted to date by industry and in the EPA's response to these test plans. Many of the test plans submitted and the EPA comments on them still call for rote, check-the-box animal testing rather than the use of "thoughtful toxicology."

In October 1999, PETA ended its grassroots campaign against the HPV Program in return for the incorporation of some minimal animal protection provisions into the program. Since that date, the EPA has failed to implement a number of the agreed-upon provisions and we have been forced to attempt to address these issues directly with the companies and consortia that are planning to conduct the testing.

Nonetheless, we appreciate the EPA's effort to integrate some of those basic animal protection concerns into the proposed test rule. The October 1999 agreement with animal protection organizations states that any subsequent test rules will proceed in a manner consistent with the animal protection principles outlined in the EPA's October 14, 1999, letter to HPV participants. Then Associate Assistant Administrator for Prevention, Pesticides, and Toxic Substances, James Aidala, assured animal protection organizations that the principles enumerated in the EPA letter to HPV participants would be incorporated into any future test rules and it is clear that, with a few notable exceptions delineated below, the EPA has made a concerted effort to do so.

At the same time, our concerns with the form and development of the original HPV program persist with the mandatory program. Section III of the preamble describes the impetus for the "voluntary" and mandatory HPV chemical-testing programs: namely that only 7% of HPV chemicals "have a full set of publicly available internationally recognized basic...effects" and that "43% have no publicly available basic hazard data." However, testimony submitted to the U.S. House Science Subcommittee on Energy and the Environment in June 1999 refutes this basis of the HPV program:

> Whereas the original EPA publications on the HPV program stated that their report on the lack of data available on HPV chemicals was a definitive study (*Frequently Asked Questions, Chemical Hazard Data Availability Study*), EPA officials now admit that it was, in fact, "a quick a dirty look in order to get the message out."
>
> [PETA and PCRM] pointed out, and then documented in a report entitled "Availability of HPV Chemical Data," that many of the chemicals had large amounts of publicly available data on them that the EPA and the EDF had overlooked. In fact, a number of chemicals on the list are substances that [were taken] off workplace shelves in the early 1980's because we were well aware back then how dangerous they were. Others have volumes of information available on them in the form of Toxicological Profiles issued by the Department of Health and Human Service's Agency for Toxic Substances and Disease Registry. Some have been in commerce since the early 1900's and have been thoroughly studied: chemicals such as turpentine, rat poison, paint thinner, and leaded gasoline.

> The Chemical Manufacturers Association study of data available on the HPV chemicals states the results of their study underestimated the amount of existing data for a number of reasons, including the fact that they were forced to consider only data that fit the narrow constraints of the screening information data set (SIDS) protocols. So, for example, 90-day chronic toxicity animal studies were ignored because the SIDS protocol calls for 14-28 day studies. According to the CMA report: "Several points need to be considered to put these results into perspective. First, lack of data electronically accessible by CAS Registry Numbers does not equate with lack of knowledge on the HPV substances...A second point to consider is that several of the test categories are inappropriate for certain HPV substances...Because HPV substances are not screened for applicability of each test category, the amount of apparently 'unavailable' data indicated by this study is most likely an overestimate. In other words, a significant fraction of the apparently 'unavailable' data is probably inappropriate or irrelevant in assessing hazards and risks...A final point is that information that was located had to meet the evaluation criteria. For example if a study administered a chemical intravenously, this study would have been rejected, even if it provided acute toxicity information." (*Public Availability of SIDS-Related Testing Data for US. HPV Chemicals*)

> The agency's newest documents on the HPV program concede that much data is, in fact, available that needs to be considered and a new term – "weight of the evidence analyses" – has now been introduced into those documents. The guidance document, *Determining the Adequacy of Existing Data*, discusses the manner in which existing data is to be considered. While we applaud the EPA for acknowledging [the existence of other data], we also note that the entire HPV program is based on the false assumption that there is no data available on these chemicals. Had the EPA considered all the data it is now telling companies to weigh, the HPV program might have taken a very different form."

Unfortunately, many redundant tests on animals are still being conducted in the HPV program. Even though sophisticated state-of-the-art knowledge exists on some of the sponsored chemicals, the "dumbed-down toxicology" data repeatedly referred to by the author of the HPV program – Ellen Silbergeld of EDF – as the specific SIDS check boxes may not. Hence, animals are being killed to test endpoints that are toxicologically, physically, or environmentally irrelevant (see, for example, test plan comments for aminosilanes), the results of which add nothing to our understanding and handling of the substance.

The "voluntary" nature of the HPV Challenge Program allowed the EPA to bypass normal government channels of public notification and peer review and hence "require" the testing of over 2100 chemicals. In section III(C), the EPA outlines the findings it must make under TSCA in order to require testing of chemicals: "The EPA must find that there is substantial release, or substantial or significant human exposure...In addition, the EPA must find that data are insufficient and testing is necessary." Section 4(a) of TSCA actually states that the EPA must demonstrate that there are insufficient data *and experience* for the effects to be reasonably determined *or predicted.* It is for this reason that the proposed test rule includes only 37 chemicals – many fewer than the more than 600 remaining "unsponsored" chemicals from the "voluntary" program.

In the same 1999 Congressional hearings, Dr. William Sanders, Director of EPA's Office of Pollution Prevention and Toxics, stated that the point of the HPV chemical-testing program was to prioritize chemicals for further testing and/or action. Section III(E) also states that this exercise will allow governments to "prioritize chemicals to

identify those which are in need of additional, more in-depth testing and assessment, as well as those of lesser concern." The undeniable fact is that this prioritization could take place now, with the current state of knowledge on many of the HPV chemicals, without killing hundreds of thousands more animals. The fact that the HPV list of chemicals still includes known-dangerous chemicals along with substances generally recognized as safe (GRAS) chemicals by the Food and Drug Administration (FDA), such as citric acid and soybean oil, is a clear indication that the EPA refuses to apply simple common sense – let alone serious scientific scrutiny – to the HPV program. As stated in one independent review of the HPV program found in *Risk Policy Report*: "We disagree very strongly with a key assumption, that in order to judge the safety of chemicals it is necessary to know the results of a standard battery of animal toxicological tests...Indulging in this rote behavior is wrong and a terrible waste of resources."

Finally, in order to avoid killing millions of animals in laboratory tests and the perception that the EPA is randomly initiating meaningless testing programs, certain principles should apply to EPA testing initiatives, whether "voluntary" or regulatory. For example, the EPA must articulate specific, discrete objectives for the programs and their roles in regulatory decision-making. In other words, the EPA should not seek to accumulate data merely for the sake of accumulating data (much of which we suspect is never even evaluated by the agency) but rather any data requested must be used to fulfill a particular regulatory or statutory goal. Further, EPA's testing programs must be integrated with international programs to ensure that duplication does not occur.

Following are our specific comments on the proposed HPV test rule.

ADOPTION OF SIDS ENDPOINTS

The *Federal Register* notice states that the EPA believes there are insufficient data to reasonably determine or predict the effects on health or the environment of the manufacture, distribution in commerce, processing, use or disposal of the 37 chemicals that are subject to the testing rule. The notice goes on to indicate that six basic testing endpoints have been adopted by the Organization for Economic Cooperation and Development (OECD) as the minimum required to screen international HPV chemicals substances for toxicity.

Prior to this rulemaking, however, the EPA has never adopted a rule requiring data on those six basic test endpoints for all HPV chemicals. Accordingly, **it is incumbent upon the EPA to articulate why these particular six endpoints are needed in order to accurately assess the hazards of the 37 chemicals that are the subject of the rule.** In section III(B) of the preamble, the EPA appears to assume that SIDS tests are equivalent to basic information on a chemical. However, some of the SIDS tests are inappropriate in characterizing some chemicals' toxicity and the SIDS battery of tests ignores much more relevant existing human and exposure data. Although the EPA claims the HPV program is based on the SIDS program, the HPV program does not require companies to submit the extensive documentation required in the OECD program which includes detailed exposure and other relevant

information such as chemical uses, sources, and human data. Without knowing OECD's basis for adopting these particular six endpoints or the EPA's rationale for not following the OECD SIDS program more closely, it is impossible for interested persons commenting on the proposed rule to gauge whether the proposed testing is in accordance with mandates of the Toxic Substances Control Act (TSCA).

Incredibly, Section IV(D) of the preamble states: "If no data are available for a [*emphasis added*] SIDS testing endpoint, there cannot be sufficient data to characterize the risk associated with exposure to the chemical." Again, no references are supplied to support this unequivocal statement which – in truth – is highly questionable.

PREAMBLE VS. TEST RULE LANGUAGE

If the EPA is truly committed to reducing the number of animals poisoned in its mandatory toxicology tests, it should use its regulatory authority in a manner consistent with that stated goal. While the preamble to the test rule contains language that addresses some animal protection concerns, that language does not also appear in the actual rule. **Since preamble language is not enforceable, the animal protection concerns should be addressed in the rule itself.**

CATEGORIES AND STRUCTURE ACTIVITY RELATIONSHIPS

The October 1999 agreement with animal protection organizations states that the principles enumerated in the October 14, 1999, letter to HPV participants will be incorporated into any subsequent test rules. The EPA's interest in promulgating an inflexible test rule (see Inflexible Test Rule comments below) is not an acceptable reason for disallowing the use of the primary methods that can reduce the number of animals killed in this testing program – namely the use of categories and structure activity relationship analyses.

Since the EPA oversees the issue of "test sponsors" – which company or consortia tests which chemical and who is provided with reimbursement – it can also oversee the application of category testing in a similar fashion.

The EPA appears to have specifically excluded the use of structure activity relationships in this test rule (Section IIID1), although it is requesting input on how to implement the application of chemical categories and structure activity relationships. Even in the short list of chemical substances in the test rule, there are some obvious compounds that would fall into existing chemical categories. For example four compounds on the list are alkyl-substituted phenol compounds that could be grouped together, including:

Compound	CAS Number
Phenol 2-(1,1 dimethylethyl)	88-18-6
Phenol, 2,4, dimethyl	105-67-9
Phenol, 2-ethyl	90-00-6
Phenol, 2,4,6-Tris(1,1 dimethylethyl)	732-26-3

A second group that could be developed might include a sulfonic acid surfactant category. Compounds in this group might include:

Compound	CAS Number
Methanesulfonic acid	75-75-2
Benzenesulfonic acid	98-11-3
Benzenesulfonic acid, hydroxy	1333-39-7

A brief review of the sponsored chemical database revealed that 22 compounds with similar structures were sponsored by a variety of groups including The Crompton Corporation, LAB Sulfonic Acids Coalition, The Soap and Detergent Association, and the American Chemistry Council. Similar chemicals that are sponsored include the almost structurally identical compounds of p,toluenesulfonic acid; xylenesulfonic acid, sodium salt; and dimethyl benzenesulfonic acid. These test plans must be coordinated by the EPA with all parties interested in these similar compounds. Failure to coordinate these individual chemicals into categories and to seriously examine test plans with the goal of preventing duplicative animal testing means that the EPA will cause many animals to die in testing simply as a result of the lack of bureaucratic coordination of test plans.

A third obvious category is to combine the two quaternary ammonium compounds listed in the test rule into a single category.

Test rule compounds that might be included in existing categories under development include dibromomethane and 1-chlorododecane which would be included with other halogenated solvents and Light Oil, coal, coke-oven which will have many proprieties in common with other heavy oil mixtures found in the petroleum industry.

EPA needs to take the lead on creating categories, and work as a liaison between industries to facilitate the inclusion of similar compounds from different industries in appropriate categories. Where existing categories do not exist, EPA should create the categories in its test rule and require significantly reduced testing to characterize a complete category. Of utmost importance and, heretofore not addressed, is the concern that the EPA must stop

considering the HPV chemicals in a vacuum and must use data-rich chemicals that are not HPV to form categories that can include HPV chemicals and thus greatly reduce the use of animals in tests.

IN VITRO GENETIC TOXICITY SCREENING

Section V(5) of the proposed rule states that "[p]ersons required to conduct testing for chromosomal damage are encouraged to use *in vitro* genetic toxicity testing." A rule is not the appropriate vehicle to "encourage" actions by regulated entities but, rather, should clearly specify the EPA's requirements. **The EPA should amend the proposed rule to mandate the use of the internationally accepted *in vitro* chromosomal aberration and gene mutation screening tests**.

The current approach allows companies to use the *in vivo* test and then submit the rationale for using animals along with the results: "A subject person who uses one of the *in vivo* methods instead of the *in vitro* method to address this end-point must submit to EPA a rationale for conducting that alternative test in the final study report." However, if the company's rationale for using animals is erroneous, there is no opportunity to spare animals from painful mammalian genetic toxicity tests. Accordingly, this sequence must be reversed. Unless a company proposing to use *in vivo* genetic toxicity testing submits compelling justification to the EPA for an exemption from the requirement to use *in vitro* tests prior to the testing being conducted, any data generated from such tests should be strictly prohibited. EPA should only grant such exemptions when the physical properties of the chemical make the use of an *in vitro* test impossible.

Similarly, the EPA must not allow submittal of a *post hoc* rationale for conducting both the repeat dose toxicity test and the reproduction/developmental toxicity screening test, rather than reducing the number of animals killed by combining the two protocols. The EPA should amend the proposed rule to require companies to use the combined protocol unless the company submits justification – in advance of initiating the testing – that documents a specific and compelling reason to test a chemical using both protocols.

The EPA has come a long way in the past two years on the issue of the use of the *in vitro* genetic toxicity screening tests. When PETA first became involved in this issue, it was the strongly held belief of EPA staff – Mr. Charles Auer, Director of the EPA's Chemical Control Division, in particular – that the *in vitro* tests could in no way substitute for the *in vivo* genetic toxicity screening test. In meetings with White House representatives, Mr. Auer insisted that the *in vitro* tests were not acceptable internationally and that Germany and Great Britain required the *in vivo* test. In fact, the opposite turned out to be true. Germany and Great Britain require the *in vitro* tests because of their greater sensitivity. The EPA eventually reversed its long held requirement that the *in vivo* test be used.

At the same, however, our repeated requests that the *in vitro* tests be required in the HPV Challenge Program were always met with the same response, namely that because the program was "voluntary", the agency could not require specific tests. This justification is disingenuous, as the agency is clearly requiring that specific tests be conducted in the "voluntary" program. However, even that rationale for merely "encouraging" the use of the non-animal tests clearly cannot apply to mandatory test rule language. We therefore again urge the EPA to require the *in vitro* genetic toxicity screening tests to be used where genetic toxicity screening tests are required in the HPV program.

ROLE OF PRODUCTION VOLUME

Throughout the HPV program and the proposed test rule (see section IIIC), the EPA claims that it is generally accepted that high production volume equates to high exposure to humans and/or the environment. Yet no references are provided for this assumption. In fact, the same 1984 National Academy of Sciences report that the EPA and EDF repeatedly referenced as a confirmatory study forming the basis of the HPV program states: "Long lists of candidate chemicals [for testing] need to be reduced to short lists through screening. Two key elements for screening are estimated human exposure and suspicion of toxic activity." According to the NAS report, volume alone should not be the criteria for wholesale testing, as it is in the HPV program. Rather, it recommends "a scientific approach based on existing knowledge of chemistry and toxicology of related compounds and likely levels of human exposure." (*Toxicity Testing: Strategies to Determine Needs and Priorities*) Both of these elements are completely missing from the HPV program. Exposure information is specifically excluded from the HPV program.

Given the fact that some of the HPV chemicals proposed for testing have been documented in the ambient and occupational environment at levels that are orders of magnitude below the recommended exposure limits, **EPA must provide references and justification for basing this program on volume of production if it is requiring testing under TSCA.**

INFLEXIBLE TEST RULE

In response to questions submitted to Dr. William Sanders by the House Science Subcommittee on Energy and the Environment following its June 1999 hearings on the HPV program, Dr. Sanders stated that "the TSCA Section 4 HPV test rule requirements are expected to be equivalent to those in the HPV Challenge Program and have never been intended to require more extensive testing." However, in discussions with then Deputy Director of the Office of Pollution Prevention and Toxics, Mr. Joseph Carra stated an opposing point of view: "There must be a clear distinction between the rule and the voluntary program. There must be advantages for companies to volunteer." This same sentiment was subsequently expressed by Mr. Auer in a meeting with Office of Management and Budget's senior domestic policy advisory on November 10, 1999.

The more inflexible the EPA makes the test rule (in order to create an incentive for companies to "volunteer") by disallowing such methods as categories and structure activity relationships (SAR's), the greater the number of animals who will die in this program. The EPA states in section III(D)(1) that "the incorporation of such elements [categories and SAR's] would require complex, time consuming, and resource intensive procedural steps, such as multi-phase rulemaking." Animals suffer and die for many stupid reasons but this has to be one of the stupidest. **The EPA must allow, encourage, and expand the use of both categories and structure activity relationships in the test rule in order to reduce the number of animals killed in this testing program** (see comments on categories and SAR's above). Both these approaches are critical to that end.

CLASS 2 CHEMICALS

The EPA has specifically requested input concerning whether it should specify the particular form of Class 2 substances that must be tested and, if so, what criteria the EPA should use to identify the representative form that should be tested. This issue demonstrates the importance of exposure data in prioritizing chemicals for testing. The most sensible approach is to require data for the composition of the chemicals that most people are exposed to and/or that is released into the environment in the largest quantity. The issue of appropriate forms of class 2 chemicals is another example of the poor conceptual design of the HPV program that excludes exposure concerns as a factor in prioritizing testing, resulting in the needless deaths of thousands of animals. The issue of class 2 chemical testing further reflects EPA's weak conceptual grasp of one of the issues associated with identifying chemical substances: the fact that CAS numbers do not necessarily describe unique chemicals, and often describe industrial process streams of similar or identical composition that are mixtures of several well-characterized compounds. Much of the EPA's consideration of class 2 chemicals toxicity ignores the first, often simple, step of carefully analyzing the composition of these substances and identifying the known bioactive agents. An example of this weakness is that the EPA is requiring testing of "Urea, reaction products with formaldehyde" without specifying that the specific composition of this complex mixture be characterized before testing begins.

ROLE OF EXISTING DATA

In addition to the comments presented here, we fully support the documentation submitted by PCRM in their comments that acute toxicity testing of a number of the HPV chemicals is wholly unnecessary and its requirement should be removed from the test rule. Acute toxicity testing should not be conducted on such substances as a component of sunscreen, a pigment for printing ink, or a naturally occurring food flavoring – all of which the EPA currently has listed as needing acute lethal dose testing on animals.

In Section III(B), the EPA states: "If relevant scientifically adequate existing data are submitted at any time before testing is initiated, including after the final rule is issued, the Agency will consider such data to determine if they satisfy the testing requirement and will take appropriate necessary action to ensure that unnecessary testing is no longer required." In order for this section to hold any meaning, test plans for chemicals to be tested under the test rule must be submitted in advance and stakeholders must be provided the opportunity to comment on them. Under the "voluntary" program, for example, General Electric stated that it had no information on three chemicals it manufactured and was planning to run the entire SIDS list of animal tests on these chemicals. We pointed out that two of those three substances were on the FDA's list of approved food contact substances and therefore data existed on those substances. The EPA was unaware of this fact.

In section III(F), the agency states that "such submissions [of data] may be made at any time to allow EPA to take appropriate action." Non-profit organizations such as PETA do not have the resources to research all chemicals in advance nor to anticipate what tests companies will propose. We are currently in the process of submitting comments on every test plan that calls for more tests on animals under the "voluntary" program. We must wait until tests are proposed on animals before researching overlooked existing data and alternative methods such as categories that could be used to reduce the number of animal tests conducted. Therefore, **test plans must be made available for public review and comment, and existing data must be used even if it is brought forward after publication of the final rule.**

The EPA must present the robust summaries upon which it based its testing requirements for the 37 chemicals. Absent this information, the public is unable to comment on existing data that has been overlooked, exposure data, or any other relevant information that could reduce the number of animal tests conducted on these 37 chemicals.

Section III(F) states that the "EPA will ensure that unnecessary testing is not required." The EPA's dismal record on this point, as documented by its comments on test plans submitted under the "voluntary" program (see Animal Welfare section below), provides no reassurance to animal protection organizations that the EPA will seriously attempt to reduce the number of animals killed in this program

Lastly, this section ignores the issue of the partial amnesty that was granted to companies in the October 14, 1999, letter to HPV participants.

REASON FOR THIS ACTION

In Section III(D), the EPA attempts to explain why the agency is proposing to take this action. The agency states that "data collected and/or developed under the HPV Initiative, when combined with information about exposure and uses, will allow the Agency to prioritize potential health and environmental effects and take appropriate follow up action." Yet in November 1999, then Associate Assistant Administrator

James Aidala stated in a speech that "HPV's screening information in most cases won't enable the EPA to promulgate risk management actions under TSCA." This is because the HPV chemical-testing program specifically excludes information about exposures and chemical uses. He further stated: "We need information like IUR data to make the HPV challenge information useful in protecting public health. Without the IUR amendments, the HPV challenge would be just a 'check-the-box' exercise."

Not mentioned in this section is a well-known reason for the initiation of the HPV program: industry and one conservative environmental protection organization put together the HPV plan with EPA's consent in order to avoid a re-examination of the Toxic Substances Control Act (TSCA), a law that is widely regarded as ineffective in protecting public health and the environment. At the 1998 "Living with TSCA" conference, Jim Quance, an official from Exxon Chemical Corporation who works as a consultant to the CMA, stated that "the top reason for companies to participate in the voluntary HPV program is to prevent reauthorization of TSCA." According to one media report, he stated that "preventing TSCA reauthorization would be the top industry-wide benefit from success of the program." (*BNA Daily Environment Report 11-19-1998*) Furthermore, the OECD SIDS program, upon which the HPV program is based, had been failing dismally prior to its resuscitation through the HPV program.

ANIMAL WELFARE SECTION

Section III(I) states that the "EPA is making every effort to ensure that as the HPV Initiative is implemented, unnecessary or duplicative testing is avoided and the use of animals is minimized." This statement is patently untrue and the wastefulness of certain animal tests conducted under the "voluntary" program has been documented repeatedly in test plan comments by the animal protection community and in letters to the agency.

Examples include: (1) the EPA has accepted test plans that ignore existing data and call for a number of check-the-box animal tests. EPA staff has stated – in direct contradiction to the original HPV framework – that existing chemical information only needs to be submitted when testing is *not* proposed. (2) The EPA is not fostering cross-industry testing of compounds, which causes repetitive testing and the use of more animals (e.g., the petroleum coke plan did not include coal coke. Light coal coke oven oil was not sponsored and could be included in an API heavy oil test plan). (3) The EPA has called for the testing of mixed composition industrial streams that are mixtures of compounds whose toxicities are well characterized (e.g., in response to the petroleum gas test plan, the EPA required testing of streams that contain ethane, propane, butane, carbon monoxide and/or hydrogen sulfide). (4) Tests are being proposed for compounds that have an extensive epidemiological and toxicological database. (5) The EPA has encouraged the development of new animal data on GRAS chemicals. (6) The EPA is allowing only a very narrow SAR approach that does not permit the use of hydrolysis effects, analytical chemical data

of complex mixtures, known realistic exposure pathways, or classic risk assessment in order to group substances together or to reduce complex compounds to fundamentally toxicologically relevant compounds.

In fact, the EPA's usual response to submitted test plans is to call for more animal testing beyond even that proposed by the submitter. The EPA's double standard regarding animal testing is obvious in the EPA's responses to proposed test plans. The EPA does not require any justification if a company wants to conduct a number of animal tests. Yet the EPA sets such ridiculously high standards each time a company proposes not to test that no company or consortia can meet that standard.

As just one example, the EPA's comments on the CMA's alkyl sulfide test plan demonstrates the EPA's presumption that more animal testing is always required and that the bar will be raised ever higher for those companies that attempt to reduce animal testing. The EPA is thus violating its own specification that "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." Further, the EPA has failed to respond officially to *any* of the specific test plan comments submitted by the animal protection community.

In Section III(I) of the test rule preamble, the EPA makes several other statements that are patently disingenuous: "The Agency is committed to replacing test methods requiring animals with alternative test methods when acceptable alternative test methods are available and to refining existing test methods to optimize animal use when there is no substitute for animal testing...EPA scientists have contributed significantly to this body of knowledge and are continuing to play a vital role by developing test methods for consideration."

Sadly, there has been minimal effort on the EPA's part in the alternatives field despite the fact that the EPA requires more chemical toxicity testing than any other federal agency. The EPA devotes virtually none of its $500 million annual Office of Research and Development (ORD) budget to researching and developing non-animal test methods. Worse, the EPA is recognized internationally as an obstacle to the adoption of replacement and refinement methods. One need look no further than the recent battle to replace the crude and cruel LD-50 test with a lethal dose test that merely reduces the number of animals poisoned to death. EPA officials were responsible for delaying that test refinement for years. Currently, one EPA official appears to be responsible for the agency's stance against a non-animal replacement test for the extremely cruel dermal penetration tests performed on animals.

While concern over animal protection issues is slowly becoming apparent at higher management levels at the EPA, it is still the case that the EPA relies almost exclusively on animal test methods. Further, many EPA staff are openly hostile and inflexible concerning the use of alternative methodologies and exhibit tremendous

ignorance in the area of non-animal methodologies, be they *in vitro* toxicity tests or simply epidemiological methods. These facts violate the implementation guidelines of the 1993 NIH Revitalization Act that states: "Agencies with regulatory programs should...reduce reliance on animal testing...Regulatory agencies with missions to protect human health and the environment need to maintain flexibility concerning new and revised methodologies that may apply to their programs." The guidelines further state that agencies should help drive the "development of novel and innovative test methods that will provide for improved risk assessment...Regulatory agency staff should be trained in the evaluation of data from newly accepted test methodologies." (NIEHS, *Regulatory Acceptance of Toxicological Test Methods*)

The EPA, through the October 14, 1999 agreement, stated its support for funding research, development and validation of non-animal, alternative test methods for integration into the HPV "voluntary" program. A commitment of $500,000 over two fiscal years was dedicated to this goal by the agency, with non-animal test replacements for the animal-based acute toxicity endpoint a priority. This goal was also reflected in the agreement which delays testing for individual chemicals sponsored under the "voluntary" program.

One year later, in October 2000, a workshop co-sponsored by the EPA and NIEHS/ICCVAM was convened to ascertain the status of assays to replace the traditional animal test used for the acute toxicity endpoint for the HPV program. Six months later the report from the workshop has not been published, nor has priority been given to further research, development and validation studies for promising test methods considered at the workshop. It is imperative that the EPA honor this commitment under the "voluntary" program and reflect the results in the final test rule. The EPA must provide all necessary resources to the ICCVAM to publish the workshop analysis, support any additional ~~research or~~ validation studies required, and sponsor the assessment of ~~validation by~~ the ICCVAM of test methods for the HPV program in an expeditious manner.

LETHAL DOSE TESTS ON ANIMALS

The proposed rule requires acute toxicity testing for 14 of the 37 chemicals included in the proposed rule. As stated above, in October 1999, the EPA agreed to spend $500,000 ($250,000 in FY 2000 and a similar amount in FY 2001) to develop and validate promising non-animal tests to be incorporated into the HPV program. These non-animal tests included the Multicenter Evaluation of *Invitro* Cytotoxicity (~~MEIC~~) human cell-line battery as a replacement for the unreliable and cruel lethal poisoning tests the EPA currently requires. These funds have not yet been spent, in clear violation of the agency's agreement with animal protection organizations. **The EPA must delay any acute toxicity testing until the non-animal method has been funded and can be used as a replacement for lethal dose tests on animals.**

See also comments in Role of Existing Data above and the comments submitted by PCRM documenting existing information on many of the 14 chemicals for which the

EPA is requiring acute toxicity testing. These comments illustrate the fact that crude lethal dose tests will not further understanding of these chemicals.

AQUATIC TOXICITY TESTING

In Section V(A)(3) of the test rule, the EPA presents its requirements for aquatic toxicity testing. *In vivo* aquatic toxicity testing is wholly inappropriate and unnecessary, given the extensive understanding of aquatic microorganims and *in vitro* test methods. Protozoan members of Ciliophora, such as the Tetrahymena, are frequently used as a measure of aquatic toxicity in ecological risk assessments. The biochemistry and physiology of Tetrahymena have been thoroughly investigated since the 1950's, and Tetrahymena have been used for aquatic toxicity testing since the 1970's. The Tetrahymena *in vitro* test is quick, easy, and cheap, and has great breadth. It allows for the examination of a large number of independent organisms that possess features of both single eukaryotic cells and multicellular organisms. Studies can easily be repeated at varying dose levels and many chemicals can be examined. 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 more expensive, time consuming, and cruel. The powerful Tetratox assay provides a more efficient and humane method to predict aquatic toxicity at the screening level.

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. Evaluation of *in vitro* and *in vivo* aquatic toxicity data have allowed researchers to develop models to predict toxicity based on SAR's. Schultz has found that most industrial organic chemicals exhibit the narcosis mode of toxic action. These toxicants are unreactive and the interaction of the toxicant with the site of action is minimal. They exhibit acute toxicities that are directly related to log Kow, regardless of molecular structure. These chemicals do not generally bind irreversibly to macromolecules or membranes, due to an absence of stereoelectronic effects. (TW Schultz, *Toxicological Methods* 7:289-309, 1997; Schultz, TW. *Chemical Research in Toxicology* 12(12):1262-7, 1999; Niculescu, Kaiser, Schultz *Archives of Environmental Contamination and Toxicology* 39, 289-298, 2000; Schultz *Bulletins of Environ Contamination and Toxicology* 65:399-406, 2000)

Some chemicals are bioreactive, and produce greater toxicity than expected, because they have the ability to have a positive stereoelectronic interaction with a biological system. Bioreactive substances can be divided into those exhibiting covalent and noncovalent mechanisms and often exhibit excess toxicity. Models can incorporate log Kow as well as measures of stereoelectric potential to predict the aquatic toxicity of various chemicals

Both the *in vitro* Tetratox assay as well as SAR's provide more humane, efficient methods to predict aquatic toxicity at the screening level and should replace the acute fish toxicity tests required in the HPV program.

TEST GUIDELINES

The tests that the EPA is requiring to be conducted under this test rule appear to be those published two weeks prior to the test rule on December 15, 2000, as "Toxic Substances Control Act Test Guidelines." These "guidelines" state: "EPA is publishing this action as a final rule without prior notice and an opportunity to comment because the Agency believes that providing notice and an opportunity to comment is unnecessary." To the best of our knowledge, many of these test guidelines have not undergone the rigorous validation procedures that all non-animal tests must undergo and we protest this continuing double standard. **Animal tests should be forced to undergo the same scientific scrutiny that non-animal tests receive and must be validated for reproducibility, reliability, and relevance prior to being required by a federal agency.**

SETBACK TO *IN VITRO* AND 'THOUGHTFUL' TOXICOLOGY

Section V(H) of the test rule preamble describes an EPA-conducted study to evaluate the capacity of testing laboratories to conduct the various tests. "The results suggest that laboratory capacity is expected to expand at a rate such that the testing that would be required by this proposed rule should be readily accommodated by testing laboratories." The fact is that the HPV program has been a windfall for animal testing laboratories including such notorious ones as Huntington Life Sciences, PLC. The HPV program has set the field of *in vitro* technology back years. In 1999, the European Centre for the Validation of Alternative Methods, an organization funded by the European Union, stated with regard to the HPV program: "Traditional toxicologists with a vested interest in the continuation of checklist animal testing, and contract testing laboratories with a commercial interest in gaining new business, must be rejoicing. This is bad news for those of use who seek a scientifically rational approach to hazard prediction and risk assessment, and the development and use of alternative methods." (*ATLA, Vol. 27*).

Also in 1999, Procter & Gamble stated in a letter to the agency: "The current approach to the HPV program continues to be focused almost entirely on a need for check-box animal and ecological testing. This approach completely discounts the many advances in toxicology and risk assessment that have been made in the past few years, particularly science based strategies that minimize the use of animals...We are very concerned that EPA will be perceived as setting back the clock by approaching the HPV chemical initiative without taking advantage of the best science available."

SUMMARY

The EPA has attempted – as promised – to incorporate some of the animal protection principles enumerated in its October 14, 1999, letter to HPV participants. However current efforts fall short and more must be done to reduce the number of animals killed in this program. In particular, the EPA must incorporate and expand the use of categories and SAR analyses in the HPV test rule, must require the use of *in vitro* genetic toxicity screening tests, must re-examine the role of production volume and exposure data, must replace the use of acute fish toxicity tests, and must delay *in vivo* acute toxicity testing.

If you have any questions, I can be contacted at 757-622-7382, ext. 1304.

Sincerely,

J. T. Sandler

Jessica T. Sandler, MHS
Federal Agency Liaison