

# **National Pollution Prevention and Toxics Advisory Committee (NPPTAC)**

February 18, 2005

Honorable Stephen L. Johnson  
Acting Administrator, U.S. Environmental Protection Agency  
1200 Pennsylvania Ave. N.W.  
Washington, DC 20460

Dear Acting Administrator Johnson,

On behalf of the National Pollution Prevention and Toxics Advisory Committee (NPPTAC), I am pleased to present to you two Committee recommendations for your consideration. The NPPTAC was established in September 2002 to provide EPA with advice, information, and recommendations on the overall policy and operations of programs undertaken by the Office of Pollution Prevention and Toxics (OPPT).

A major program effort in OPPT is the High Production Volume (HPV) Challenge Program, a unique and important cooperative effort involving EPA, chemical producers and public interest groups. A key component of this effort is a commitment to assemble, analyze, and make publicly available a core of data and information relevant to assessing the human health and environmental hazards of chemicals produced in very large quantities.

NPPTAC is considering options for addressing HPV data, and formed an HPV Work Group to assist in preparing the Committee to make informed recommendations in the HPV area. The NPPTAC held a public meeting on February 10, 2005 during which the HPV Work Group reported to the Committee on potential EPA actions to consider. The Committee deliberated and adopted the formal recommendations for a High Production Volume (HPV) Chemical Screening Process and Guidance for Preparing the Final Category Analysis that I present to you here.

On behalf of the Committee, I thank you for the opportunity to participate in EPA's policy and program activities through the NPPTAC, and for considering these recommendations.

Sincerely,

A handwritten signature in black ink that reads "Harry E. Gregori, Jr." in a cursive style.

Harry E. Gregori, Jr., AICP  
Co-Chair

Enclosures

cc: NPPTAC Members

**National Pollution Prevention and Toxics Advisory Committee (NPPTAC)**  
**Recommendation to the U.S. Environmental Protection Agency on the**  
**High Production Volume Challenge Program:**  
**HPV Chemical Screening Process**

February 10, 2005

The High Production Volume (HPV) Challenge Program is a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds each year. The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is expected to begin evaluating the data submissions on approximately 1,400 sponsored chemicals by the beginning of 2006. Each completed submission contains data on 18 internationally agreed to "SIDS" (Screening Information Data Set) endpoints that are used as screening-level indicators of potential hazardous effects (toxicity) for humans or the environment, as well as environmental fate.

NPPTAC recommends that OPPT implement the HPV chemical screening process as described in the attached document *HPV Chemical Screening Process*, which was developed by the NPPTAC's HPV Work Group. The purpose of the screening process is to help OPPT order its review of the data in Challenge Program submissions and to provide structure to a review process for determining hazard potential for substances sponsored in the HPV Challenge Program. The key features of the screening process are:

**Tier I: Automated Screening:** Tier I is an automated process in which key endpoint data are screened against predetermined criteria to establish a logical order in which OPPT should review the chemicals/categories. Tier I accepts data generated by the HPV Challenge Program at face value, and there is no evaluation of the quality or completeness of the data in Tier I. The results of Tier I do not provide a final judgment of hazard or risks, if any, of a chemical/category. The screening criteria are based largely on the hazard criteria used in the Globally Harmonized System (GHS) for the Classification and Labeling of Chemical Substances. The Work Group has reached consensus on the use of the screening criteria in all but one case. As described on page 6 of the document referenced above, the Work Group did not reach consensus on how to sort chemicals that (a) are initially placed in the third review group based on the toxicity criteria alone and (b) fail both of the environmental fate criteria. The HPV Work Group recognizes that such decisions will therefore be left to OPPT.

**Tier II. Manual Review and Characterization:** In Tier II OPPT would conduct a more in-depth review of the data in the Challenge Program submissions for quality and completeness; develop a screening level hazard assessment based on SIDS and non-SIDS hazard data provided by the sponsors; and inform the sponsors and the public of its findings. Tier II review could potentially include additional or updated hazard information of which EPA and/or sponsors or other parties have become aware. Any use and exposure information in the submission should be described to assist in any further information gathering, assessment, or management activities that OPPT deems appropriate. However, Tier II is not an evaluation of the exposure potential or risks of a chemical. Finally, the hazard assessment should note situations where the Tier II review has revealed that a chemical is potentially persistent or potentially bioaccumulative.

There are a variety of post-Tier II actions available to OPPT that support voluntary or regulatory hazard communication and risk management activities.

OPPT should complete Tier II for those chemicals in the first review group in approximately 2 years and for all HPV Challenge Program chemicals in approximately 4 years. The NPPTAC urges the Administrator to ensure that resources are sufficient to meet this time line.

OPPT is requested to report back to NPPTAC on results and actions resulting from this recommendation and at that time the Committee will consider if further advice or recommendations are appropriate.

## HPV Chemical Screening Process

### Background

The High Production Volume (HPV) Challenge Program is a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds each year. In the Challenge Program, U.S. producers and importers of HPV chemicals voluntarily sponsor chemicals. Sponsorship entails the identification and initial assessment of the adequacy of existing information, the conduct of new testing (if adequate data do not exist), and making the new and existing test results available to the public.

The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is expected to begin formally evaluating the data submissions on approximately 1,400 sponsored chemicals by the beginning of 2006.<sup>1</sup> Each completed submission contains data on 18 internationally agreed to "SIDS" (Screening Information Data Set) endpoints that are used as screening-level indicators of potential hazardous effect (toxicity) for humans or the environment, as well as environmental fate.

The HPV Challenge Program Work Group was asked by the National Pollution Prevention and Toxics Advisory Committee (NPPTAC) to develop and propose a hazard-based screening process to organize the chemicals in the submissions received through the HPV Challenge Program and guide their further review by OPPT. The process consists of two tiers, which are described below and in the attachments to this document.

### Tier I: Automated Sorting of HPV Chemicals

Tier I is an automated process whereby key elements of a submitted data set are screened against predetermined criteria to establish a logical order in which OPPT should review the chemicals/categories. *The results of Tier I do not provide a final judgment of hazard or risks, if any, of a chemical/category.* Tier I screening is a sorting process to guide the sequencing of OPPT's chemicals assessment and management work. Tier I accepts data generated by the HPV Challenge Program at face value; there is no evaluation of the quality or completeness of the data. Quality and completeness of the submitted data set and its toxicological meaning are assessed in Tier II (see below).

Many of the criteria used in the Tier I screen for human health effects, ecological effects, and environmental fate endpoints are based on the hazard classification criteria used in the Globally Harmonized System (GHS) for the Classification and Labeling of Chemical Substances.<sup>2</sup> The proposed screening process criteria and their use for sorting chemicals is described in Attachment A. A trial use of the Tier I screen on 53 HPV submissions indicated that approximately 55% of the submissions may go into the first review group (Attachment B). OPPT staff have indicated that this portion of chemicals in the first review group would not jeopardize their ability to review the data sets generated by the HPV Challenge Program in a timely manner. It is noted, for example, that for pre-manufacture notifications, OPPT conducts similar reviews for over 1,000 chemicals each year.

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<sup>1</sup> OPPT has reviewed each robust summary for hazard information that might indicate the need for expedited review.

<sup>2</sup> OECD SERIES ON TESTING AND ASSESSMENT Number 33. 14Aug2001. *Harmonised Integrated Classification System for Human Health and Environmental Hazards of Chemical Substances and Mixtures*. See [www.oecd.org/LongAbstract/0,2546,en\\_2649\\_34365\\_2671862\\_1\\_1\\_1\\_1,00.html](http://www.oecd.org/LongAbstract/0,2546,en_2649_34365_2671862_1_1_1_1,00.html).

## **Tier II: Manual Review and Characterization of Hazard Data in HPV Challenge Program Submissions**

The purpose of Tier II is for OPPT to conduct a more in-depth review of the data contained in HPV Challenge Program submissions, develop a screening level hazard assessment based on data provided by the sponsors, and inform the sponsors and the public of their findings. Tier II represents the first time that data are not accepted at face value and as such incorporates a scientific review of all endpoint data in each submission. The Tier II review typically does not look beyond the data provided by the sponsors; however, it could potentially include additional or updated relevant hazard information of which EPA and/or sponsors or other parties have become aware of during this process. Attachment C contains additional detail on the types of activities OPPT should undertake in the Tier II process.

Because exposure information was not required under the HPV Challenge Program, the amount of exposure information in the HPV submissions is limited. Thus, Tier II is not an evaluation of the exposure potential or risks of a chemical. An exposure evaluation, if needed, occurs subsequent to the Tier II hazard assessment. However, any supplemental information voluntarily submitted by the sponsor regarding use and exposure should be described to assist in any further information gathering, assessment, or management activities that OPPT deems necessary. The hazard assessment should also note situations where the Tier II process has revealed that a chemical is potentially persistent or potentially bioaccumulative.

The key outputs of a Tier II review are a determination as to the adequacy of the submitted data and a screening-level hazard characterization that is posted in the public HPVIS database. The public, including sponsors, would be allowed to offer comments on the hazard assessments, and those comments would be posted in the HPVIS as well. The hazard characterizations that emerge from Tier II will serve as important information tools for OPPT's existing chemicals management processes.

### **Post Tier II Activities<sup>3</sup>**

The key output of Tier II is a screening-level characterization of the hazards of each chemical sponsored in the HPV Challenge Program. This information is an essential component of a sound and comprehensive process for the safe management of existing chemicals. Nevertheless, hazard information alone is generally considered an insufficient basis for the initiation of risk management. However, when combined with other information, especially the potential for exposure to the chemical, the resulting information can form the foundation for a range of possible follow-up actions.

In those cases where the Tier II evaluation raises specific questions, or suggests a need for further inquiry, there are a large number and range of follow-up actions available to OPPT that would support voluntary or regulatory hazard communication and risk management activities. Such actions could include:

- gathering additional information on uses (e.g., by use function, category, release potential, or benefit) and exposure (to humans and/or the environment);
- gathering additional information on hazards to support a more in-depth characterizations;
- identifying existing risk management programs and practices;
- evaluating existing Federal and State regulatory controls (e.g., occupational exposure limits);

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<sup>3</sup> "Post-Tier II" does not imply that OPPT must complete the Tier II evaluation of all chemicals before initiating actions described here. Ideally, subsequent actions would be proposed shortly after completion of the hazard assessment.

- providing information referrals or recommendations for actions to other EPA program offices or other Federal or State agencies;
- initiating a risk assessment led by EPA, another agency, industry, etc.;
- referring the chemical to another program or agency for assessment; or
- deciding after closer examination that no further action is needed at this time.

In cases where the results of the Tier II evaluation suggest the need for additional information, the following general approaches are recommended:

- Review the entire Challenge Program submission. Hazard characterizations are made largely on the basis of information in robust study summaries. However, many sponsors included a large range of potentially relevant information with their initial test plan, final category report, or in other correspondence. Consequently, EPA and other users of information from the HPV Challenge Program are encouraged to first consider all information provided prior to initiating follow-up activities.
- Communicate directly with sponsors. A key lesson from the Challenge Program is that a large amount of relevant information may exist with chemical manufacturers outside of the public domain. Therefore, where the Tier II evaluation identifies a need for specific information that was not provided in the course of the Program, OPPT is encouraged to communicate directly with sponsors to determine whether needed information is readily available. The inquiries (and any information subsequently provided) should be made public in a manner consistent with the protection of intellectual property, as described in current EPA regulations.
- To the extent feasible, solicit information on other assessments or risk management activities already underway within industry, in other EPA offices or State or Federal programs, or in other countries.
- Conduct initial assessments as efficiently as possible, and make results (including the basis for and nature of both decisions entailing further review/action and decisions that no further review is necessary) transparent and publicly available.
- Based on the activities described in the previous bullets, consider the full range of voluntary and regulatory measures available gather further information and to identify and manage risks posed by the use of a chemical, and select approaches that can provide risk-based improvements in human health or the environment.

## ATTACHMENT A. GUIDANCE FOR SORTING CHEMICALS FOR FURTHER REVIEW

This draft sorting system employs three sets of criteria described below, which relate to human health effects, ecotoxicity, and environmental fate. The results of Tier I do not provide a final judgment of hazard or risks, if any, of a chemical/category. In Tier I, each chemical is ultimately assigned to a first, second, or third priority group for further review by OPPT in a stepwise process. First, it is determined whether the chemical exceeds any of several human health and ecotoxicity criteria. Each chemical receives a separate review group assignment for human health and ecotoxicity. The higher of these two assignments is carried forward. Next, if the chemical exceeds criteria concerning potential persistence or bioaccumulation, its review group assignment can be adjusted upward, as described below. The data used for this screen are the hazard-level screening data provided by sponsors in the U.S. High Production Volume Challenge Program. Where sponsors have used ranges of values to report on an endpoint, both in single chemical submissions and for members of a category, the screen should employ the most conservative value within the stated range.

### HUMAN HEALTH CRITERIA

**Endpoints:** Repeat Dose Toxicity (primary), genetic toxicity (both gene mutation and chromosomal aberration), reproductive toxicity, and developmental toxicity.

**Step 1.** Use Globally Harmonized System (GHS) for the Classification and Labeling of Chemical Substances<sup>‡</sup> to determine GHS Category based on repeat dose toxicity LOAEL (Lowest Observed Adverse Effects Level) for the relevant route of exposure.

First Group:	GHS Category 1
Second Group:	GHS Category 2
Third Group:	Does not meet GHS Category 2 criteria

#### GHS Repeat Dose “Guidance Doses/Concentrations” for 90-day Studies.

Criteria values should be tripled for chemicals evaluated with 28-day studies.

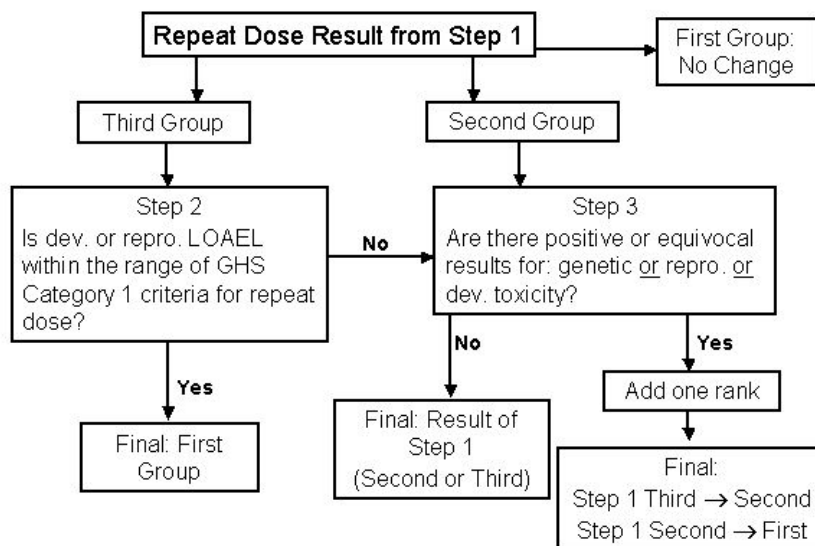
Route of exposure	Units	Category 1 (First Group)	Category 2 (Second Group)
Oral (rat)	mg/kg bw/d	< 10	10-100
Dermal(rat or rabbit)	mg/kg bw/d	< 20	20-200
Inhalation (rat) gas	ppm/6h/d	< 50	50-250
Inhalation (rat) vapour	mg/litre/6h/d	< 0.2	0.2-1.0
Inhalation (rat) dust/mist/fume	mg/litre/6h/d	< 0.02	0.02-0.2

**Step 2.** This step accounts for situations in which the reproductive or developmental effect is observed at much lower doses relative to the repeat dose effect. For chemicals placed in the third review group in Step 1, if either the reproductive or developmental LOAEL is within the range of the GHS Category 1 criteria, the chemical is considered to be in the first group for human health. Otherwise, go to step 3.

**Step 3.** This step allows for modification of the initial repeat dose classification for chemicals that exhibit genetic, reproductive, or developmental toxicity. For chemicals placed in the second or third review group in Steps 1 and 2, if one or more endpoints among genetic, reproductive, or developmental toxicity are positive, the chemical goes to the next highest review group. Otherwise, result from applying the repeat-dose criteria in Step 1 remains unchanged. For this purpose, equivocal results are considered positive.

<sup>‡</sup> GHS Reference: OECD SERIES ON TESTING AND ASSESSMENT Number 33. 14Aug2001. *HARMONISED INTEGRATED CLASSIFICATION SYSTEM FOR HUMAN HEALTH AND ENVIRONMENTAL HAZARDS OF CHEMICAL SUBSTANCES AND MIXTURES.*

The following diagram illustrates Steps 2 and 3.



## ECOTOXICITY CRITERIA

**Endpoints:** Acute fish, acute daphnia, and algal toxicity (three different endpoints).

Follow GHS criteria for LC<sub>50</sub> or EC<sub>50</sub> (median lethal concentration or effective concentration for 50% of the test population) as follows:

First Group	< 1 mg/L
Second Group	1 – 10 mg/L
Third Group	> 10 mg/L

## ENVIRONMENTAL FATE CRITERIA

**Endpoints:** Log K<sub>ow</sub> (octanol/water partition coefficient) and OECD ready biodegradation test.

The criterion used for Log K<sub>ow</sub> (>4) is the same as that used in the GHS, and the Organization for Economic Cooperation and Development (OECD) has established the basis for the ready biodegradability test as less than 60% mineralization to CO<sub>2</sub> in 28 days.

Environmental fate can modify the results obtained from applying the toxicity criteria (see table below). A chemical that was placed preliminarily in the second or third review group as a result of applying the human health and ecotoxicity criteria is moved one group “higher” if it exceeds the criteria for either of the environmental fate endpoints. A special case exists when a chemical placed in the third review group exceeds the criteria for both of the environmental fate endpoints, as shown in the table below.

Preliminary Review Group Based on Toxicity ↓	Final Review Group After Applying Environmental Fate Criteria		
	Fails Log K <sub>ow</sub> Criterion Only	Fails Biodegradation Criterion Only	Fails Both Log K <sub>ow</sub> AND Biodegradation Criteria
First	First	First	First
Second	First	First	First
Third	Second	Second	<i>First or Second</i>

The HPV Work Group was not able to come to consensus regarding the review group to which chemicals that exceed the criteria for both ready biodegradability and log K<sub>ow</sub>, but do not exceed criteria for health or ecotoxicity endpoints, should be assigned. Work Group members were of two perspectives: that such chemicals should be placed in the first review group or that such chemicals should be placed in the second review group. Reasons articulated for including such chemicals in the first review group include:

- The screening-level toxicity data included in SIDS are quite limited, and hence leave substantial uncertainty regarding toxicity, especially for chronic and sub-chronic endpoints, which are of most concern for persistent and/or bioaccumulative chemicals.
- The potential for persistence and bioaccumulation are chemical properties relevant to both human and environmental health risk, as is their potential, especially in combination, to result in high exposure to such chemicals if they are released into workplaces or the environment.
- Tier I should avoid producing false negatives, even at the risk of producing false positives, because the latter will be identified in Tier II.
- Many, if not most, known chemicals of widespread concern possess these properties, which have led to widespread environmental contamination and exposure, only after which did a full understanding of their toxicity emerge.
- Given the limits to our current knowledge, these chemicals should be given the same priority for review as chemicals with evidence of toxicity, but not persistence or bioaccumulation potential, based on the SIDS tests.

Reasons articulated for including such chemicals in the second review group include:

- Chemicals exhibiting evidence of toxicity warrant a higher priority review than those that do not, based on the SIDS test data.
- The SIDS battery employed in the HPV Challenge Program does not show evidence of toxicity for such chemicals, and both toxicity and exposure are needed to produce risk.
- Such chemicals will be stigmatized despite no evidence of toxicity.
- The SIDS tests for these endpoints, especially the ready biodegradability test, are overly conservative and produce too many false positives.
- Assigning a high priority status to such chemicals will place too many chemicals in the first review group and thereby undermine the utility of the screening process as a management tool.

The HPV Work Group recognizes that the decision about into which review group such chemicals should be placed will therefore be left to OPPT. In making such a decision, the HPV Work Group recommends that OPPT review all of the information contained in the sponsor's submission and any additional information that may come to light during the review process.

## ATTACHMENT B. SUMMARY RESULTS OF APPLYING THE SCREENING CRITERIA

	No. (%)
First Review Group	29 (55%)
Second Review Group	9 (17%)
<i>First or Second Group</i>	4 (8%)
Third Review Group	6 (11%)
Unable to Sort	5 (9%)
Total	53

See notes at the end of the table for explanation of notations.

No.	Human Health		Ecotoxicity Group	Environmental Fate Modification?	FINAL
	Initial Repeat Dose Toxicity Group	Final Health Effects Group			
8	2	1	3	N	1
9	3	2	3	Y	1
10	3	3	3	Y	1 or 2
14	3	2	3	Y	1
16	3	2	3	Y	1
18	3	2	3	N	2
22	2	1	N/A (I)	N	1
23	3	2	3	N	2
25	U	2	3	Y	1
26	2	1	2	N	1
39	2	2	3	Y	1
54	1	1	1	N	1
69	3	2	3	N	2
72	3	2	1	N	1
74	1	1	1	N	1
91	2	1	2	N	1
104	3	2	3	Y	1
108	1	1	3	N	1
112	3	3	3	Y	1 or 2
131	2	2	3	N	2
175	3	3	3	Y	1 or 2
183	CSI	-- (T)	-- (D)	N	—
189	T	2	2	N	2?
193	2	1	2	N	1
195	T	—	3	N	3?
214	3	3?	3	N	3?
217	-- (T)	-- (T)	-- (T)	N	—
218	CSI (D)	-- (D/T)	-- T	N	—
228	1	1	1	N	1
230	-- (T)	-- (T)	2?	Y	1
235	3	3	1	N	1
238	2 (CSI -D)	2?	2	Y	1
240	T	-- (T)	T	N	—
241	T	-- (T)	1?	N	1
246	1	1	3	N	1
267	3	3	3	Y	1 or 2

No.	Human Health		Ecotoxicity Group	Environmental Fate Modification?	FINAL
	Initial Repeat Dose Toxicity Group	Final Health Effects Group			
272	2	1	1	N	1
283	3	3?	2	Y	1
284	3	2	3?	Y	1
294	3	3?	1	N	1
295	2	1	N/A	N	1
305	3	3	3	N	3
306	3	3	3	N	3
307	CSI	2	2	N	2
309	T	--(T)	3?	Y	2
311	T	--(T)	T	N	—
313	D	—(D)	3	N	3?
317	3	3	3	N	3
320	2	1	2	N	1
328	D	2	3	Y	1
329	3	3?	3?	Y	2
337	3	2	3?	N	2
344	2	1	3	N	1

**Explanations for NOT ranking 5 of the 53 chemicals:**

No. 183 – CSI chemical; testing proposed on other major endpoints.

No. 217 – No data available; testing proposed on all endpoints.

No. 218 – CSI chemical (EPA disagrees with CSI claims); testing proposed on other major endpoints.

No. 240 – No data available (except Log  $K_{ow}$ ); testing proposed on all other endpoints.

No. 311 – No data available (except Log  $K_{ow}$ ); testing proposed on all other endpoints.

**Key**

Priorities: 1 – First Review Group; 2 – Second Review Group; 3 – Third Review Group

? – Because testing is proposed on these chemicals (either on one or more endpoints), the ranking may or may not change once data are received.

CSI – Chemical is a Closed System Intermediate. Thus, the requirement for repeat dose and reproductive toxicity data are waived.

D – EPA disagrees

(D) – Cannot rank because EPA disagrees

(D/T) Cannot rank because EPA disagrees and testing is proposed

(I) – Inadequate data

N/A – Not applicable

T – Testing proposed

(T) – Cannot rank because testing proposed

U – Unable to test

**ATTACHMENT C. ACTIVITIES OPPT SHOULD UNDERTAKE IN ITS TIER II REVIEW**

1. **Conduct an objective evaluation of the quality and completeness of the data set in the HPV Challenge Program submission.** If the submission is determined to be complete, OPPT should inform the sponsor and the public that OPPT believes the sponsor has fulfilled its commitment to the HPV Challenge Program for that compound or category. If OPPT believes that the submission is incomplete, it should attempt to reconcile data gaps in collaboration with the sponsor. It should be noted that OPPT conducts such reviews when it comments on a sponsor's initial test plan. However, some portions of final submissions will not necessarily have had such review. Any subsequent data provided should be made public in the same manner as data submitted earlier, consistent with the protection of intellectual property, as described in current EPA regulations. OPPT's evaluation should observe the following:
  - For each SIDS endpoint, a Robust Summary submitted by the sponsor should provide data in sufficient detail to permit the reviewer to determine that the data are adequate and sufficient to support the conclusions contained within the document.<sup>4</sup>
  - If more than one available study is relevant to an endpoint, and one study is selected over the others, the basis for that selection should be presented in a transparent manner, and its selection justified. Criteria for selection should be consistent for all submissions. The justification narrative should present and discuss the degree of concordance across studies in the same species, or across species. If there are conflicting data, this should be stated and used to assess uncertainty and the need for additional studies. In general, the most sensitive effect and test system should be used for each SIDS endpoint, unless there is a sound, scientific basis for the use of another study.<sup>5</sup>
2. **Independently assess the submitted data for each SIDS endpoint to determine the level of hazard.** If EPA finds that there is insufficient information to draw a conclusion about an endpoint, or if OPPT disagrees with any conclusions drawn by the sponsor, the basis for this finding should be stated clearly. This disagreement should be communicated to the sponsor and the public with a desired goal being to reconcile the disagreement through the collaborative process employed in the HPV Challenge Program to date. In situations where appropriate additional tests may reduce the uncertainty, OPPT should identify those tests.
3. **Develop a hazard characterization of the substance(s).** The hazard characterization should be developed using current OPPT hazard assessment guidelines that consider the relative mammalian and aquatic toxicity of each substance, including the number of test systems in which the chemical exceeded criteria cutoff values, the magnitude by which each value is exceeded, and the substance's environmental fate characteristics.<sup>6,7</sup>

OPPT may determine that, based on the available hazard data, a chemical requires no further review. In such cases, the chemical should be designated as "No Further Hazard Characterization Required at This Time" with respect to hazard. Further review can be triggered at any time in the future as deemed appropriate by OPPT when additional information on hazard, use, or exposure becomes

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<sup>4</sup> *Draft Guidance on Developing Robust Summaries*, October 22, 1999. See [www.epa.gov/chemrtk/robsumgd.htm](http://www.epa.gov/chemrtk/robsumgd.htm).

<sup>5</sup> *Determining the Adequacy of Existing Data*, February 10, 1999. See <http://www.epa.gov/chemrtk/datadfin.htm>

<sup>6</sup> See EPA's Risk Assessment Forum at <http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=55907>.

<sup>7</sup> *Guidance for Risk Characterization*, February 1995, U.S. EPA Science Council. See <http://www.epa.gov/osa/spc/htm/rcguide.htm>.

available, a novel new use is proposed, there is a substantial increase in use, or other relevant information prompts review.

- 4. Incorporate the OPPT Tier II findings in the portion of the public HPVIS database that contains the HPV chemical or category submission.** As noted above, OPPT's findings should include its quality and completeness assessment and its hazard characterization, as well as: 1) a description of any use and exposure data provided by the sponsor and 2) a data needs assessment, if appropriate. The data needs assessment should indicate the type of information (additional hazard data or use and exposure information) needed to help OPPT effectively assess and manage risk.

Data in the HPVIS database should be updated appropriately (e.g., upon reconciliation of sponsor/EPA disagreements).

**National Pollution Prevention and Toxics Advisory Committee (NPPTAC)**  
**Recommendation to the U.S. Environmental Protection Agency on the**  
**High Production Volume Challenge Program:**  
**Guidance for Preparing the Final Category Analysis**  
February 10, 2005

The High Production Volume (HPV) Challenge Program is a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds each year. The Challenge Program has allowed and encouraged sponsors to group HPV chemicals into proposed categories of chemicals when it is scientifically defensible to do so. Under the category approach, groups of chemicals thought to be structurally similar and to share similar chemical properties, or for which chemical properties are thought to vary in a predictable pattern based on chemical structure, are considered together rather than separately. About 80% of the chemicals sponsored in the Challenge Program have been submitted as part of a chemical category.

NPPTAC recommends that OPPT consider and transmit to category sponsors the supplemental guidance for preparing a Final Category Analysis as described in the attached document *Guidance for Preparing the Final Category Analysis*, which was developed by the NPPTAC's HPV Work Group. The purpose of this additional guidance is to ensure that all data, including those newly generated, affirm the justification for the formation of the category and that the data on individual category members provided in the Final Category Analysis will be compatible with the High Production Volume Information System (HPVIS).

Basic elements of the Final Category Analysis guidance include:

- A (re)statement of the definition and justification for the category that reflects all available data, including any new test data or estimated values developed through execution of the sponsor's test plan;
- A thorough explanation of the method(s) of data derivation (i.e., extrapolation/interpolation) and rationale used by the sponsor to provide a value (or range of values) for each relevant endpoint for each untested category member; and
- A completed data matrix that provides the full data set for all category members for all relevant endpoints, including an explanation for how all extrapolated/interpolated values (or range of values) were derived.
- In some cases, categories may warrant case-by-case consultation between the sponsor and OPPT in order to derive an acceptable category data matrix.

This recommendation also applies to the use of surrogate chemicals. Sponsors should provide the same elements described for the Final Category Analysis for those endpoints for which data from the surrogate are being used.

EPA is requested to promptly consider this recommendation and communicate its Final Category Analysis guidance to sponsors. EPA is also requested to report back to NPPTAC on results and actions resulting from this recommendation and at that time the Committee will consider if further advice or recommendations are appropriate.

## Guidance for Preparing the Final Category Analysis

### **Background**

The HPV Work Group was asked by the National Pollution Prevention and Toxics Advisory Committee (NPPTAC) to develop for NPPTAC consideration approaches for addressing the use of chemical categories in the HPV Challenge Program. The Challenge Program has allowed and encouraged sponsors to group HPV chemicals into proposed categories of chemicals when it is scientifically defensible to do so. Under the category approach, groups of chemicals thought to be structurally similar and to share similar chemical properties, or for which chemical properties are thought to vary in a predictable pattern based on chemical structure, are considered together rather than separately. In such cases, generally not all chemicals need a complete set of test data in order to address all health and environmental endpoints, the idea being that data available for some chemicals in the category for a given endpoint can be used to estimate or otherwise infer (e.g., through interpolation or extrapolation, often called “read-across”) the analogous values for related category members that lack such data.<sup>1</sup>

The motivations for the category approach are three-fold: to reduce the use of laboratory animals to address animal welfare concerns; to reduce testing costs to industry; and to increase the number of chemicals that can be considered within a given amount of time and given resources. To date, the US HPV Challenge Program has made quite extensive use of categories, with the sponsors of the test plans for about 80% of the chemicals for which such plans have been submitted proposing to consider the chemicals as members of categories.

In 1999, EPA issued draft guidance governing the use of chemical categories in the Challenge Program.<sup>2</sup> That draft guidance anticipates and briefly addresses steps that should be taken by the sponsor of a proposed chemical category to fulfill its sponsorship obligation, namely: (1) re-assess the validity of a category it proposed, based on all data available after completion of any proposed testing; (2) if found not to be supported by the data, either revise and re-propose the category, subdivide the category into smaller categories that are supported by the data, or provide test data on each endpoint for each chemical; and (3) ultimately provide a complete set of screening-level hazard values for each endpoint for each member of the proposed category, whether derived from existing data or application of category-based non-testing methods (e.g. read across), or new testing.

There is general agreement within the HPV Work Group that completion of a category proposal requires, whether through provision of a new document or revision of an existing document, a final accounting by the sponsor that affirms the category and carries out the category analysis. EPA’s draft guidance refers to a “category analysis document” to be submitted by the sponsor,

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<sup>1</sup> In some cases, specific qualitative or quantitative relationships have been developed that correlate chemicals’ structures with specific chemical properties, including in some cases health and environmental endpoints. These relationships are termed structure-activity relationships, or SARs. Sometimes these relationships allow derivation of a mathematical model, called a quantitative SAR or QSAR. The output of such SARs and QSARs is an estimated value for a given endpoint for a given chemical, based on input values for that same chemical or other chemicals. SARs and QSARs are among the methods that can be employed in a category approach to provide estimated values for untested category members.

<sup>2</sup> See [www.epa.gov/chemrtk/categuid.htm](http://www.epa.gov/chemrtk/categuid.htm).

but the content of that document and its relationship to the other required documents – the original and revised test plans and the robust summaries – has yet to be specified in any detail. Because some sponsors already have indicated that they believe their work is finished, the HPV Work Group considers the development of guidance to be a priority matter, and this document provides clarity on the elements of the Final Category Analysis. In doing so, this document also ensures that data contained in the Final Category Analyses will be compatible with the High Production Volume Information System (HPVIS) in order to facilitate examination of the data generated by the HPV Challenge Program.

The HPV Work Group considered the existing guidance and the need to promote high quality program results while not creating unnecessary additional burdens on sponsors. The HPV Work Group recognizes that the specific approach used to “fill in” endpoints within the category data matrix will depend on the type of category, category rationale, and endpoint. In that regard, the following additional guidance is suggested as to the important elements of a Final Category Analysis.

Finally, the HPV Work Group recognizes that a great deal of work has been done by the Organization for Economic Cooperation and Development (OECD) with regard to category analysis, and the OECD is in the final steps of finalizing its category analysis guidance.<sup>3</sup> The principles outlined in this document are consistent with the OECD guidance, and OPPT should use the OECD guidance as a supplement to the guidance provided in this document.

### **Elements of the Final Category Analysis Document**

- A (re)statement of the definition and justification for the category that reflects all available data, including any new test data or estimated values developed through execution of the test plan. Any change in the category definition or justification from that provided in the original test plan, and how any chemicals removed from or added to the category are to be assessed, should be explained.
- A thorough explanation of the method(s) of data derivation (i.e., extrapolation/interpolation) and rationale used by the sponsor to provide a “value” for each relevant endpoint for each untested category member using the data available for the tested members.
- A completed data matrix that provides the full data set for all category members for all relevant endpoints. This matrix should include assignment of an appropriate value to each cell of the matrix. Each value in the final data matrix should be accompanied by an indication of how it was derived (i.e., measured data, estimate derived from applying a SAR/QSAR, read-across, etc.):
  - For category members not tested directly, the format/form (including units as applicable) in which the interpolated/extrapolated/estimated values for a given endpoint are

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<sup>3</sup> Organization for Economic Cooperation and Development. 2004. Draft Revision of the Guidance Document for the Formation and Use of Chemical Categories. ENV/JM/EXCH/SIAM(2004)6. OECD does not expect to receive substantial comments on this draft. A final guidance will likely be published as a chapter in the forthcoming *OECD Manual for the Investigation of HPV Chemicals*.

expressed should match the format/form of the measured values for that same endpoint for the tested category members. The appropriate format/form will vary with endpoint and method of interpolation/extrapolation/estimation, but may include a single quantitative value, a maximum value (e.g., <X), a minimum value (e.g., >Y), a range (e.g., between X and Y), or, where appropriate, a qualitative descriptor (e.g., readily biodegradable, positive/negative). If a quantitative value or range can be provided, it should be, barring a compelling justification as to why it should not be.

- The interpolated/extrapolated values provided should be “stand-alone,” and should not require accessing analogous data for other category members in order to be understood or interpreted. For example, use of a term such as “similarly toxic” should be avoided; rather, the quantitative value or range of values for the tested category member(s) serving as the basis for the interpolated/extrapolated value should be what is inserted into the matrix cell for the untested category member.
- Complex mixture and/or Class 2 substance (i.e., substances of unknown or variable composition) categories may warrant case-by-case consultation between the sponsor and OPPT in order to derive an acceptable category data matrix.

### **Surrogate Chemicals**<sup>4</sup>

An issue closely related to the use of categories is the use of so-called “surrogate chemicals” – chemicals not formally included in a category but judged to be sufficiently similar to an individual chemical or a category so that their test data on one or more endpoints can be used to interpolate/extrapolate values to the sponsored chemical/category members. In such cases, the same elements described above for the category analysis document should be provided for the use of surrogates (unless already provided in the original test plan): an explicit justification for the selection and use of the surrogate for the relevant endpoints; a description of how values for the sponsored chemical(s) have been interpolated/extrapolated from the surrogate(s); and a data set that includes the actual interpolated/extrapolated values and indicates their source.

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<sup>4</sup> The term “surrogate chemical” as used here is synonymous with the terms “supporting chemical” and “analogue.”