Final Report to the New England Waste Management Officials Association

Using the HPVIS to Identify the Next Generation of Persistent Bioaccumulative Toxic Substances

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Introduction

Since 2003, the Environmental Working Group (EWG) has acquired and compiled 80 chemical toxicity, testing, and regulatory databases from government, academic, and industry sources into an in-house, integrated Chemical Information System. This integrated database allows EWG to systematically evaluate potential health and environmental concerns for chemicals detected in food, tap water, air, and the human body. Over the past two years EWG has focused on adding new databases to this in-house resource that allow for systematic identification of chemicals that potentially meet national and international criteria that define PBT (Persistent, Bioaccumulative, Toxic) chemicals – toxic compounds that persist in the environment and accumulate in wildlife or humans. And most recently, through a grant from the Northeast Waste Management Officials Association (NEWMOA), EWG has acquired and attempted to integrate the U.S. Environmental Protection Agency's (EPA) High Production Volume Information System (HPVIS). This database houses basic screening studies and indicator parameters on the properties and toxicity of chemicals produced in or imported into the U.S. in volumes exceeding one million pounds annually.

The objectives of our NEWMOA-funded analysis of the HPVIS data were twofold. First, we assessed the usability of the database. Secondly, we assessed the content of the database, comparing data housed in this resource against data contained in other resources in EWG's integrated Chemical Information System. Specifically, we conducted this comparison for five chemicals selected as test cases. We assessed the scope of data on persistence, bioaccumulation, and toxicity within HPVIS in an effort to understand the limitations EPA will face if the Agency attempts to use this database to assess potential exposure risks or to inform public health policy.

Our analysis of the HPVIS data shows that companies appear to be selectively entering findings from relevant, available studies. Data are not comprehensive, are not always accurate, and do not appear in every case to capture the full range of test results in the literature. And from this preliminary review, it appears that the HPVIS data are not of sufficient quality or scope to serve as EPA's submission to OECD's Screening Information System (SIDS).

Background: EWG's Chemical Information System

EWG's Chemical Information System includes government, industry, and academic data sources that collectively define chemical nomenclature, properties, hazard classifications, toxicity/fate testing and modeling results, test availability, use and production, and regulatory status. This database uses primarily Chemical Abstract Registry Numbers (CASRN's) as the unique chemical identifiers that connect the disparate data sources into a single integrated system. Other data types were connected using the SIDS templates (OECD 2004) as a guide. These data sources include individual listings on nearly 250,000 unique chemicals, chemical groups and other hazardous agents. For this NEWMOA-funded project we compared data in HPVIS against the data contained in the other resources within our Chemical Information System, primarily from the following eight sources:

- International Uniform Chemical Information Database (IUCLID 2000)
- ECOTOX (ECOTOX 2006)
- Environmental Fate Database (EFDB) (EFDB 1982)
- Registry of Toxics Effects of Chemical Substances (NIOSH 2006)
- Model Data from EPISuite (USEPA 2000)
- Model and experimental data from Environment Canada (EC 2006)[1]
- OSPAR Convention for the Protection of the Marine Environment of the North-East Atlantic (OSPAR 2002; OSPAR 2005)
- Nordic Substances Database (NSDB 2003)

Barriers in acquiring and assessing the HPVIS data

The HPVIS database proved a challenge to import into our in-house Chemical Information System. We attempted to import it in three ways. None of our efforts were successful and we have yet to integrate a user-friendly, internally consistent version of HPVIS into our Chemical Information System. Methods we used in attempts to import the data are described below.

- **Construction of database via Robust Summaries.** Before EPA released their online query system, we sought to manually construct a database of tests recorded in the HPVIS Robust Test Summary documents. We first explored constructing a database by reading the summary documents and recording the test results contained in them, but this task proved to be too resource intensive. We then tried to automate identifying and storing test data from the summary documents through simple text recognition programs developed at EWG. This proved unfeasible: the data in the Robust Test Summary documents are not standardized, but instead appear in many different formats, making automated data extraction

[1] The Canadian model data was officially published in July 2006. However, the models and data have been released in part beginning 2003.

impossible.

- **Oracle export.** We acquired an Oracle export of the HPVIS data from EPA in September 2006. The exported files proved to be missing tables and could not be re-imported into the EWG Oracle installation, presumably because of differences in Oracle versions (Personal versus Enterprise). We did not attempt to acquire the data *en masse* from EPA in an alternate form, but instead attempted a third method intended to expedite the process of our acquiring the data, described below.

- **Downloads of tabular queries.** Finally, we successively download tabular queries of EPA's HPVIS online database. When we assessed the downloaded data, however, we found that the exported information failed to preserve the data structure and field delimiters, making interpretation and parsing of the download difficult. More importantly, in many cases data contained in downloaded records were different from data in records online through EPA's query system.

We further reviewed the downloaded data to assess the quality of the HPVIS data, and found two notable problems. First, we found a number of records that include multiple test results embedded in text fields with multiple references. The Robust Summaries are designed to house a single numerical test result for each record; multiple results should be separated into multiple records. Unless EPA separates test results into unique fields, these composite text records would require further, manual separation for the data to be useful in systematic assessments.

Second, and perhaps more importantly, units and unit formatting are not consistent across the same endpoints, also making systematic evaluation of the data difficult. EWG is in the process of developing a robust tool to recognize and convert data types and units, a method we've used successfully with other datasets. Completion of this unit conversion tool for the HPVIS data proved to be outside the scope of this project. We plan to continue this work, and expect that it will ultimately allow us to convert HPVIS data to a set of consistent units, and to finally have a useable form of HPVIS in our integrated, Chemical Information System. But EPA must also develop standardized units to improve the utility of the database to the Agency and others.

Assessing the Scope and Quality of HPVIS data

Approach. We had initially sought to systematically compare HPVIS data on persistence, bioaccumulation, and toxicity against all data available from other databases in EWG's integrated Chemical Information System, to determine if the scope of data contained in HPVIS captures a representative cross section of available studies. Such a comparison would have allowed us to assess potential limitations EPA will face if the Agency attempts to use HPVIS data to assess risks or inform policy.

Because we were not able to develop a useable form of the database, however, we instead selected five chemicals covered in the HPVIS database to serve as test cases in addressing the issue raised above. Specifically, we assessed five PBT-related parameters or data types included in the HPVIS: partition coefficients, bioaccumulation, biodegradation, ecotoxicity, and mammalian toxicity as described by the following Screening Information Data Set (SIDS) test methods:

- SIDS 2.5: n-Octanol/water partition coefficient (K_{ow})
- SIDS 3.5: Biodegradation
- SIDS 3.6: Bioaccumulation (BCF/BAF) – Note: This information was not explicitly required under the HPV Challenge Program for all chemicals, but because the chemicals in this study have all been identified as PBTs by one or more regulatory bodies, we would expect to see them (or QSARs) because of the requirements of SIDS 4.6: Toxicity to Terrestrial Organisms.
- SIDS Chapter 4: Ecotoxicity
- SIDS Chapter 5: Mamalian Toxicity

The five chemicals that served as test cases in our assessment are listed below. These chemicals encompass a range in the weight of the evidence for persistence and bioaccumulation, and include known PBTs, chemicals strongly suspected to be PBTs, potential PBTs with mixed data or equivocal data, and substances where the EWG database is not well populated.

Chemical name and weight of evidence on PBT properties	**CAS RN**	**Abbreviation**
1.) phenol, 4(1,1,3,3 tetramethylbutyl) OR **tert-octylphenol (mixed or equivocal PBT data)**	140-66-9	t-OP
2.) 1,5,9-cyclododecatriene **(a potential PBT)**	4904-61-4	CDT
3.) 1,2,5,6,9,10-hexabromo-cyclododecane **(a potential PBT)**	3194-55-6 25637-99-4	HBCD
4.) Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo- OR **tetrabrombisphenol A (a known PBT)**	79-94-7	TBBPA
5.) Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl)- OR **4-sec-Butyl-2,6-di-tert-butylphenol (very little PBT data available)**	17540-75-9	4BTBP

Cyclododeca-1,5,9–triene (CDT) and 1,2,5,6,9,10 hexabromocyclododecane (HBCD) have received a great deal of attention lately to HBCD's potential as a PBT (Law, Kohler et al. 2005; Covaci, Gerecke et al. 2006; Covaci, Voorspoels et al. 2006) and Davis, et al (Davis, Gonsior et al. 2005; Davis, Gonsior et al. 2006) CDT as a degradation product HBCD (of which there are several isomers).

Phenol, 4(1,1,3,3 tetramethylbutyl) also known as **tert-octylphenol (tOP)** is a known food additive and has received some attention as a potential weak endocrine disruptor (Pedersen, Christiansen et al. 1999; Willoughby, Sarkar et al. 2005; Bangsgaard, Madsen et al. 2006).

Tetrabrombisphenol A (TBBPA) was designated under the Toxics Release Inventory and Waste Minimization Program (USEPA 1998; USEPA 1999).

4-sec-Butyl-2,6-di-tert-butylphenol [4BTBP] is a alkylphenol where we have less data than others (such as Phenol, 4(1,1,3,3 tetramethylbutyl)), so the HPVIS has the potential to add significantly to the body of available information.

For each of these chemicals, we compared the number of unique studies in EWG's Chemical Information System to the total number available in the HPVIS dataset. We also compared the range of results for each endpoint in HPVIS against the range reflected in the EWG Chemical Information System.

Results. We analyzed tests covering a total of 25 parameters (5 endpoints for each of the 5 chemicals), and found the following:

- For all 5 chemicals we identified studies from other sources for at least one parameter with results falling outside the bounds of data included in HPVIS, often indicating a higher level of hazard than HPVIS data:
    - For 4 out of 5 chemicals the persistence, bioaccumulation, or toxicity studies not included in HPVIS gave results reflecting a hazard more than 1 order of magnitude higher than results included in the HPVIS database.
    - For 52% of the parameters we assessed (13 of 25), HPVIS failed to capture the upper-bound (higher hazard) test information reflected in other data sources.

  We did not conduct a detailed literature review for each of the five chemicals assessed, but constrained our analysis to data included in other database sources. Therefore, the full scope of gaps in HPVIS data are likely greater than what is expressed above.
- One chemical, hexabromocyclododecane, was subject to a literature review of the data (Law, Kohler et al. 2005) in July 2005, one week after the final robust summary was submitted. Our review of data sources cited in this 2005 literature review shows that fully 13 of 35 relevant peer-reviewed toxicity studies available

by the end of the 2004 were not included in the robust summary.

- For all its apparent omissions, HPVIS also contained data not included in other sources. Forty-four percent of HPVIS endpoints contained information not included in other datasets.

Regarding basic data on the health and environmental effects, the following should be noted:

- HPVIS fails to include results from many studies in other standard databases. In general, the studies within HPVIS do not capture the full range of test results available, and in particular do not capture studies that reflect upper-bound estimates of hazard.
- HPVIS integrates some recent and previously unpublished studies not in other databases. The HPV Challenge Program appears to have spurred some new testing of HPVs, or submission of existing, previously unpublished data.
- Although HPVIS data are better organized than data contained in the EU's IULCID system, many toxicity endpoints remain embedded in text fields, reducing the utility of the information.
- Bioaccumulation data are not required under the HPV program, and are not always included in robust summaries, but these data are required under the SIDS program. Companies' failure to provide bioaccumulation data for many sponsored chemicals in HPVIS will reduce the databases' utility to serve as SIDS submissions.
- HPVIS often fails to include chemical use and exposure data detailed in the Robust Summaries.
- We identified errors in the database that indicate a need for a robust review of the data by EPA. For instance, we identified instances where study results appear more than once in the database, and we found cases in which units are inaccurate.

Discussion and Conclusion

A company's sponsorship of a chemical in the HPV program involves a commitment to summarize relevant, existing data. Yet for the parameters we assessed, we found that companies have not met this commitment. If HPVIS is to be used by the Agency and others as a screening tool to assess potential risks and to inform policy, it is critical that the full range of data be included in the database. It will be difficult for EPA to verify that companies are providing the full scope of data for the many thousands of sponsored chemicals.

EPA has proposed that data within the HPVIS be used to fulfill US commitments under the international Screening Information Dataset (SIDs) for High Production Volume (HPV) chemicals program. But because our assessment indicates that the data may be

grossly incomplete, the HPVIS data will be inadequate as a standalone dataset for the generation of SIDs data.

Although we recommend further assessment of HPVIS data, our limited review reveals that the studies and industry comments in the robust summaries submitted to the HPVIS provide a selective assessment of chemicals rather than a thorough compilation of available data.

Recommendations and Follow Up

Suggested improvements to HPVIS structure. We recommend that the EPA and industry improve the HPVIS in the following ways:

- EPA should provide the HPVIS data in a format that is accessible to the public. We were able to develop an in-house, electronic version of this database only after time-intensive manipulations of the raw data, and continue to manipulate and correct the data to make it useable.
- The database should include test results for structurally similar chemicals in cases where tests for the subject chemical are not available.
- The database should include information linking parent chemicals and degradation products to eventually allow for the data to be more effectively used as a screening tool to identify chemicals in commerce that may pose concerns.
- The database should include a consistent system for representing units of measure in studies that are represented in the database.
- The database should use a standard referencing system. As it stands, formats for referencing vary widely.

Suggested improvements to HPVIS content. We recommend that the EPA and industry improve the content of the HPVIS database in the following ways:

- Companies should provide a full and complete representation of relevant, available studies.
- EPA should thoroughly review the data entered by companies to ensure that it is accurate and complete.

The results of this study were presented at the "Characterizing Chemicals in Commerce" Conference December 12-14, 2006 in Austin, TX.

PARTITION COEFFICIENTS

Chemical		**EWG's Chemical Info System**	**HPVIS**	**Major data gaps in HPVIS**	**New data in HPVIS**
t-OP	Experimental	3 – 5.31 (6 studies)	4.12 (1 study)	X	
	Model	5.28 – 5.31 (2 studies)	5.28 (1 study)		
CDT	Experimental	3 - 6.19 (4 studies)	4.97 (1 study)	X	
	Model	5.48 (1 study)	None		
HBCD	Experimental	5.81 (1 study)	5.63 (1 study)		
	Model	7.74 1 study	None		
TBBPA	Experimental	3 – 5.9 (3 studies)	4.54 – 5.90 (2 studies)		
	Model	6.3 – 7.2 (2 studies)	None		
4BTBP	Experimental	None	None		
	Model	6.43 (1 study)	6.43 (1 study)		

BIOCONCENTRATION FACTORS

Chemical		**EWG's Chemical Info System**	**HPVIS**	**Major data gaps in HPVIS**	**New data in HPVIS**
t-OP	Experimental	113 - 469 (2 studies)	None	X	
	Model	2291 – 45,700 (6 studies)	None		
CDT	Experimental	2630 – 14800 (2 studies)	None	X	
	Model	3467 (1 study)	1339 (1 study)		
HBCD	Experimental	18,100 (1 study)	8974 (1 study)	X	X
	Model	6166 (1 study)	None		
TBBPA	Experimental	20 – 1200 (4 studies)	148 – 3190 (5 studies)		X
	Model	5 – 42,700	None		
4BTBP	Experimental	None	None	X	
	Model	6310 – 1,400,000	None		

BIODEGRADATION

Chemical		**EWG's Chemical Info System**	**HPVIS**	**Major data gaps in HPVIS**	**New data in HPVIS**
t-OP	Ready	0.0% - 74%: 28 days (3 studies)	0.0% - 69.9%: 28 – 35 days (3 studies)		
	Inherent	Not inherent (5 studies)	None		
CDT	Ready	0.0% – 2%: 5 – 14 days (1 study)	1%: 28 days (1 study)		X
	Inherent	Not inherent (1 study)	None		
HBCD	Ready	Not ready (1 study)	0.0%: 28 days – 100%: 7 days (6 studies)		X
	Inherent	None	None		
TBBPA	Ready	0.0%: 80 days - <20%:28 days (4 studies)	0.0%: 14 days – 60%: 64 days (7 studies)	X	X
	Inherent	Not inherent (6 studies)	Yes (1 study)		
4BTBP	Primary	Weeks (1 model)	Weeks (1 model + read-across)		
	Ultimate	Months (1 model)	Months (1 model + read-across)		

ECOTOXICITY

Chemical		**EWG's Chemical Info System**	**HPVIS**	**Major data gaps in HPVIS**	**New data in HPVIS**
t-OP	Acute – LC50	0.069 mg/L: 24 hours, shrimp - 81.0 mg/L: 48 hours, fish (25 studies)	0.019 mg/L: 96 hours, shrimp – 4.2 mg/L: 72 hours, algae (4 studies)		X
	Chronic – NOEC	0.0061 mg/L: 60 days, trout – 0.030 mg/L: 21 days, daphnia (2 studies)	0.0061: 60 days, trout - <1 mg/L: 35 days trout (3 studies)		
CDT	Acute – LC50	0.116 mg/L: 24 hours, goldfish – 140 mg/L: 96 hours, algae (7 studies)	0.47 mg/L: 96 hours, mysids – 140 mg/L: 96 hours, algae (4 studies)	X	
	Chronic – NOEC	None	None		
HBCD	Acute – LC50	0.0093 mg/L 72 hours, algae – 146 mg/L: unknown time, daphnia (5 studies)	0.0093 mg/L: 72 hours, algae – >1.5 mg/L: 96 hours, algae	X	X
	Chronic – NOEC	None	128 mg/kg: 56 days, worm – 250 mg/kg: 28 days, earthworm (2 studies)		

ECOTOXICITY

Chemical		**EWG's Chemical Info System**	**HPVIS**	**Major data gaps in HPVIS**	**New data in HPVIS**
TBBPA	Acute – LC50	0.0016 mg/L: 96 hours, zebra danio – 8.2 mg/L: unknown time, killifish (15 studies)	0.4 mg/L: 96 hours, trout – 8.2 mg/L: 48 hours, killifish (5 studies)	X	
	Chronic – NOEC	0.16 mg/L: 35 days, minnow – >0.98 mg/L: 21 days, daphnia (4 studies)	0.16 mg/L: 35 days, minnow - >0.98 mg/L: 21 days, daphnia (3 studies)		
4BTBP	Acute – LC50	0.072 mg/L: 96 hours, fish – 0.22 mg/L: 48 hours, daphnia (model study)	0.003 mg/L: 90 days, fish – 0.008 mg/L: 21 days, daphnia (model study)		
	Chronic – NOEC	0.003 mg/L: 90 days, fish – 0.008 mg/L: 21 days, daphnia (model study)	0.003 mg/L: 90 days, fish – 0.008 mg/L: 21 days, daphnia (model study)		

MAMALIAN TOXICITY

Chemical		**EWG's Chemical Info System**	**HPVIS**	**Major data gaps in HPVIS**	**New data in HPVIS**
t-OP	Acute	25 – 4600 mg/kg (12 studies)	>2000 mg/kg – 2200 mg/kg (4 studies)	X	
	Multiple Dose	32 – 7680 mg/kg (24 studies)	2000 mg/kg (1 study)		
	Reproductive	250 – 1920 mg/kg (2 studies)	200 ppm (1 in vivo study)		
	Developmental	0.014 (1 study)	75 – 750 mg/kg (2 read across		
	Mutagenic	Negative (3 in vitro studies)	Negative (3 in vivo studies)		
	Tumorgenic	5280 mg/kg (1 study)	None		
CDT	Acute	500 – 4660 (4 studies)	none	X	X
	Multiple Dose	10,700 mg/kg (1 study)	None		
	Reproductive	None	100 – 300 mg/kg (1 study)		
	Developmental	None	25 ppm (1 study)		
	Mutagenic	Negative (2 in vitro studies)	None		
	Tumorgenic	None	None		
HBCD	Acute	> 10,000 mg/kg (1 study)	> 10,000 mg/kg (3 studies)		X
	Multiple Dose	None	2650 – 4820 mg/kg (4 studies)		
	Reproductive	None	> 1000 mg/kg (1 study)		
	Developmental	> 2500 mg/kg (1 study)	>1000 - >2500 mg/kg (2		
	Mutagenic	None	> 2000 mg/kg (1 in vivo + 3 in vitro studies)		
	Tumorgenic	None	> 4000 mg/kg (1 study)		
	Neurological	None	> 1000 mg/kg (1 study)		

MAMALIAN TOXICITY

Chemical		**EWG's Chemical Info System**	**HPVIS**	**Major data gaps in HPVIS**	**New data in HPVIS**
TBBPA	Acute	3160 – 5000 mg/kg (5 studies)	2000 – 5000 mg/kg (5 studies)	X	X
	Multiple Dose	2500 – 100,000 mg/kg (4 studies)	780 - >2500 mg/kg (6 studies)		
	Reproductive	250 mg/kg (1 study)	> 1000 mg/kg (2 studies)		
	Developmental	10,000 mg/kg (1 study)	None		
	Mutagenic	Negative (1 in vitro study)	None		
	Tumorgenic	None	None		
4BTBP	Acute	None	4800 mg/kg (1 study)		X
	Multiple Dose	None	1.08 – 100 mg/kg (4 read across)		
	Reproductive	None	15 – 750 mg/kg (2 read across)		
	Developmental	None	75 – 750 mg/kg (2 read across)		
	Mutagenic	None	Negative (5 in vitro)		
	Tumorgenic	None	none		

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