United States Environmental Protection Agency

Office of Pollution Prevention and Toxics

ChemRTK Home

HPV Challenge Program

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DEVELOPMENT OF CHEMICAL CATEGORIES IN THE HPV CHALLENGE PROGRAM

I. *Introduction*

Under EPA's High Production Volume (HPV) Challenge Program the chemical industry is being challenged to voluntarily compile a Screening Information Data Set (SIDS) on all chemicals on the US HPV list. The SIDS, which has been internationally agreed to by member countries of the Organization for Economic Cooperation and Development (OECD), provides basic screening data needed for an initial assessment of the physicochemical properties, environmental fate, and human and environmental effects of chemicals. The information used to complete the SIDS can come from either existing data (including published or unpublished data on the same or analogous substances or from new tests conducted as part of the HPV Challenge Program.

The Challenge Program is designed to develop screening-level hazard information on about 2,800 HPV chemicals which were reported for the Toxic Substances Control Act's 1990 Inventory Update Rule (IUR). More information on this list can be obtained at *http://www.epa.gov/chemrtk/hpvchmlt.htm*. The large number of chemicals to be tested makes it important to reduce the number of tests to be conducted, where this is scientifically justifiable. One approach is to consider closely related chemicals as a group, or category, rather than test them as individual chemicals. In the category approach, not every chemical needs to be tested for every SIDS endpoint. However, the test data finally compiled for the category must prove adequate to support a screening-level hazard assessment of the category and its members. That is, the final data set must allow one to assess the untested endpoints, ideally by interpolation between and among the category members. In certain cases, such as where toxicity does not change among tested category members, extrapolation to the higher category members may be acceptable.

The use of categories is encouraged in the Challenge Program and will have a number of benefits. First, the public will be informed earlier about any

hazards of HPV chemicals when category testing can be completed sooner than individual tests for each chemical given that the CMA Framework recommends that categories be handled in the first two test years of the Challenge Program. Second, there is an economic savings since less testing may be needed for chemicals considered as a category. Third, a reduction in testing will result in fewer animals used to test a category of chemicals as opposed to doing each test on each individual chemical. Finally, category proposals may be expanded via the inclusion of: (1) HPV chemicals on the 1994 IUR (see http://www.epa.gov/chemrtk/volchall.htm.); (2) appropriate non-HPV chemicals that may have relevant data; and (3) chemicals in the OECD SIDS program, thereby gaining future efficiencies.

EPA has developed this guidance document to assist industry participants and others in constructing and supporting categories for the Challenge Program. Because this is a complex area, category proposals may need to be reconsidered as data become available in the Challenge Program; where needed, such an iterative process will help to ensure scientifically acceptable results consistent with the original premise for the category. This document will be updated as new experiences are gained through the Challenge Program.

II. *DEFINITIONS*

A chemical category, for the purposes of the Challenge Program, is a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. These structural similarities may create a predictable pattern in any or all of the following parameters: physicochemical properties, environmental fate and environmental effects, and/or human health effects. The similarities should be based on the following:

•a common functional group (e.g., aldehyde, epoxide, ester, etc.); **or**

•the likelihood of common precursors and/or breakdown products, via physical or biological processes, which result in structurally similar chemicals (e.g., the "family approach" of examining related chemicals such as acid/ester/salt); **and**

•an incremental and constant change across the category (e.g., the dimethylene group difference between adjacent members of the alpha-olefins - see Appendix). Within a category different members can be selected for the endpoint desired - i.e., those selected for a category approach for environmental effects endpoints may not be suitable for assessing human health effect endpoints.

Categories can sometimes apply to series of chemical reaction products or chemical mixtures that are, again, related in some regular fashion. Analogous to the basic “discrete chemical” category model, in a mixture category some, but not all, of the individual mixtures may undergo testing. The **Appendix** presents an OECD SIDS category made up of linear alkylbenzene mixtures. This is a relatively simple example of the type of approach that can work in the Challenge Program. As experience is gained in dealing with more complex mixtures, additional EPA guidance for mixture categories will be forthcoming.

Categories accomplish the goal of the Challenge Program - to obtain screening level hazard information - through the strategic application of testing across the category. If these test results show that the chemicals in the category behave in a similar or predictable manner, then interpolation and/or extrapolation can be used to assess the chemicals in lieu of conducting additional screening-level testing.

III. *GENERAL APPROACH FOR DEVELOPING CATEGORIES FOR THE HPV CHALLENGE PROGRAM*

Developing HPV Challenge categories can be considered a stepwise process (see Figure 1 for a schematic of the process and the Appendix for an example).

Step 1: Develop a potential category by grouping a series of like chemicals. A category definition should describe the molecular structure a chemical must have to be included in the category including criteria such as carbon chain length, functionality, chemical or metabolic equivalence considerations, etc., and must list the specific substances covered. Consideration and rationale should be given for using a structure-activity relationship (SAR) approach to identify related members in the category (e.g., a series of acids and their corresponding salts, a list of alkenes or petroleum streams). Some category members need not be HPV chemicals, however, their presence and associated data might help describe the category for that endpoint.

Step 2: Gather published and unpublished literature on physicochemical properties, environmental fate and effects, and health effects for each member of the category. This should include all existing relevant data and not be limited to the SIDS endpoints (e.g., metabolism and cancer studies are relevant but not part of SIDS). Literature searches may include unpublished data from non-U.S. producers and importers.

Step 3: Evaluate available data for adequacy. Please see EPA guidance document on Data Adequacy (*http://www.epa.gov/chemrtk/guidocs.htm*).

Step 4: Construct a matrix of SIDS endpoints vs. category members arranged in molecular weight order (or some other fashion indicating the structural progression of the category). Indicate in the cells of the matrix whether data are available or unavailable. An example of a completed matrix appears in the alpha-olefins example in the Appendix.

Step 5: Evaluate the data to determine whether there is a correlation among category members and each SIDS endpoint. The same category members do not have to be used for each evaluation , i.e., the members selected for environmental fate may be different from those used to evaluate toxicology effects.

A. If there are substantial data, i.e., adequate data for a given SIDS endpoint, but no apparent pattern, the proposed category may not be appropriate and so testing may be required for all remaining category members for that SIDS endpoint. However, an alternative category proposal may be developed (go back to Step 1).

B. If there are substantial and adequate data that correlate well with structure, the category may be appropriate and the sponsor prepares a category proposal (Step 6).

C. If substantial and adequate data do not exist, but the sponsor believes the structure-based category is valid for one or more SIDS endpoints, then a category approach may still be proposed (go to Step 6).

Step 6: Category rationale and testing scheme will be made available for review using the test plan formats such as those that are available in the U.S. Tracking System (http://www.hpvchallenge.com), or in the ICCA (International Council of Chemical Associations) Tracking System (http://www.icca-chem.org)(see Appendix for examples of category test plans). While sponsors are ultimately responsible for the success of their category proposals, EPA's position on individual proposals will reflect its need to anticipate the acceptability of the results in EPA's own chemical assessment programs and in OECD SIDS as appropriate.

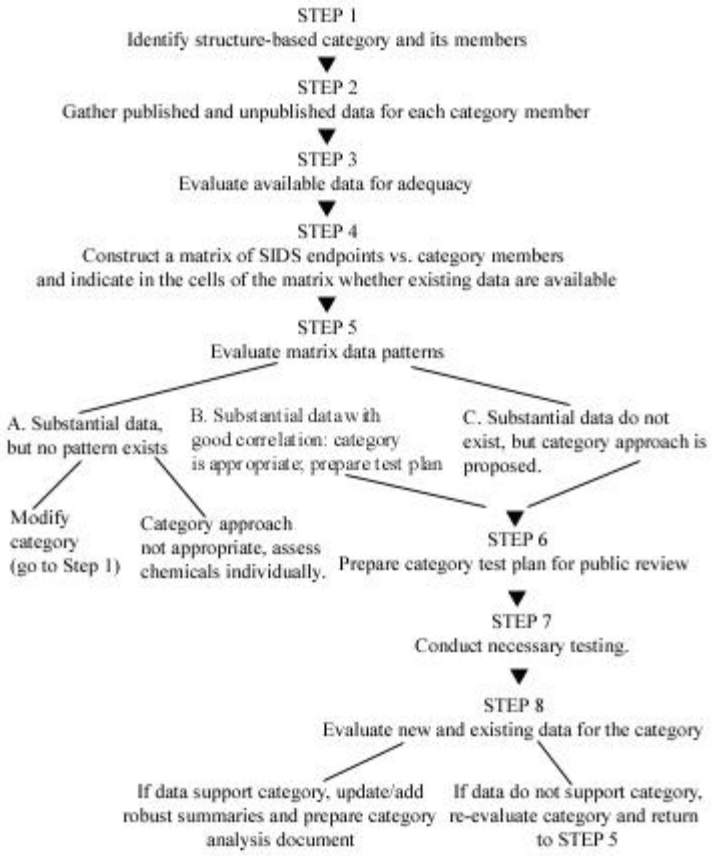
Step 7: Conduct the necessary testing.

Step 8: Add the new data to the matrix and evaluate whether the existing data and the new data support the proposed category.

A. If the results support the category, the testing phase is complete. Sponsors then update/add the appropriate robust summaries and prepare a category analysis document. The category analysis document would include a summary of the one or more SIDS endpoints in which the category "holds", including the interpolation/extrapolation of test results to the remaining, untested matrix cells.

B. Otherwise, the sponsor must consider whether to revise the category (return to Step 5). Such a revision could include further testing and/or changing or dropping members of the category, dividing the category as appropriate, or dropping the category approach altogether. The latter implies that testing will then be done to fill all appropriate SIDS endpoints for each category member.

FIGURE: Proposed Process for Developing Categories for the HPV Challenge Program



IV. *CONTENT OF CATEGORY TEST PLANS*

Category test plans should include a category definition, rationale, and testing scheme (see example category test plans in the Appendix and at the following websites: http://www.hpvchallenge.com and http://www.icca-chem.org). The rationale supporting a category definition should be as simple and transparent as possible, and should explain why the existing data and proposed testing data in the matrix would allow interpolation or extrapolation to other cells in the matrix that have no data or proposed testing. The testing scheme considers the adequacy of the existing data, and how the proposed testing

will adequately characterize the category.

Thus, an acceptable category test plan will consist of a matrix of category members and SIDS endpoints and some cells in this matrix must be filled with sufficient data. Assuming the SIDS endpoints are rows in the matrix, each row must have data in at least one cell. Assuming the columns are the category members, one or more columns may have all empty cells.

V. *EVALUATION AND CLOSURE OF CATEGORY APPROACH: THE CATEGORY ANALYSIS*

Once the testing proposed for the category is completed, an evaluation is done to determine whether the new data support the proposed category. This evaluation will be in a category analysis document. This document will serve as a summary of the new and existing robust summary data, coupled with any interpolation/extrapolation used for one or more of the SIDS endpoints, that support or refute the proposed category.

VI.*EPA'S EXPERIENCE IN DEVELOPING CATEGORIES FOR TESTING PURPOSES*

OECD experience provides a framework for handling categories under the Challenge Program. That experience is limited, however, and the Challenge Program will take up numerous issues that will expand that experience. Within the OECD's Working Party on Existing Chemicals, the US has agreed to take lead responsibility for developing the category concept. Thus, lessons learned in the US and contributed to the OECD will provide a measure of feedback and review.

The largest categories in the OECD SIDS program to date contain eight to ten chemicals. This is not a formal maximum, but acceptable categories will tend to be self-limiting because structural variation cannot be pursued indefinitely without disturbing endpoint trends and because large categories will tend to be unwieldy in general. In this regard, approaches could consider groups of related individual categories as contributing elements in the design and implementation of an overall strategy. However, a more populous category may be justifiable in certain cases, such as when toxicity of the category is generally low.

The Appendix contains a number of examples of how a category approach has been taken for the purpose of collecting, reporting, and assessing hazard information in the OECD SIDS program.

Other examples of categorizing chemicals for hazard assessment purposes include the CONCAWE (the European oil company organization for environment, health and safety) approach of categorizing chemicals in petroleum streams (CONCAWE, 1998), and approaches to assess the ecotoxicity (Bowmer et al., 1998) and health effects (Clary, et al., 1998) of lactate esters.

VII REFERENCES

Bowmer, CT, RN Hooftman, AO Hanstveit, PWM Venderbosch and N van der Hoeven. 1998. The ecotoxicity and the biodegradability of lactic acid, alkyl lactate esters and lactate salts. Chemosphere (37)(7):1317-1333.

Clary, JJ, VJ Feron and JA van Velthuijsen. 1998. Safety assessment of lactate esters. Regul. Tox. and Pharm. (27):88-97.

CONCAWE. 1998. Heavy Fuel Oils Product Dossier, No. 98/109. CONCAWE, Brussels, May, 1998. (NOTE: Heavy Fuel Oils is one of the 11 product groups identified by CONCAWE. Their address is CONCAWE, Madouplein 1, 1210 Brussel, Belgium. Their website is http://www.concawe.be).

APPENDIX

Abbreviated Examples of Category Justifications

Examples presented in this **Appendix** are drawn from the OECD SIDS program. They are modified to meet the purposes of presenting an example for the US HPV Challenge Program. The examples follow the steps for identification and development of categories noted in the main text of this guidance (see **Figure 1 in main text)**. The examples are:

- A. Alpha-olefins - discrete chemicals with an incremental and constant change across the category;
- B. Linear alkyl benzenes - family of mixtures; and

C. Brominated diphenyl ethers - family of congeners.

Example A: Alpha Olefins Series

Step 1: Identification of structure-based category. The category was defined as olefins bearing a single medium-length, even-numbered, unbranched aliphatic chain with no other functional groups ("•-Olefins"). This category consists of discrete chemicals with an incremental and constant change across its members (dimethylene group). Because the double bond is terminal, possible metabolic reactions such as oxidation at the double bond or allyl position should not be unduly affected by the chain lengthening. The lower (C_6) and upper (C_{14}) boundaries were based on the available product lines of the sponsors involved in the OECD effort.

The chemical structure of the category is:

R = CH_3, n-Propyl, n-Pentyl, n-Heptyl, n-Nonyl

Step 2: Gather published and unpublished literature for each member of the category. A literature search resulted in identifying a significant amount of available data for most category members in most of the major SIDS endpoints.

Step 3: Evaluate available data for adequacy. The sponsor evaluated available data, at the individual study level, collected for each member of the category. Available data were compiled and included all SIDS endpoints and other relevant information; non-SIDS data were found and used in the hazard profile (e.g., aspiration hazard potential to humans).

Refer to the EPA guidance on Data Adequacy (*http://www.epa.gov/chemrtk/guidocs.htm*) for more information on this issue.

Step 4: Construct a matrix of SIDS endpoints indicating available/adequate data. Table A-1 is a matrix of SIDS endpoints and available/adequate data for each member of the alpha-olefin category. For simplicity, not all relevant data are presented.

Step 5: Evaluate matrix data patterns. The information in Table A-1 identifies where data gaps (noted as "-" in the table) exist. Note that adequate data (noted as "√" in the table) are available for most endpoints. Endpoint data were evaluated to determine whether they correlate with chemical structure to judge the acceptability of the category. Although not shown in Table A-1, the data suggested that water solubility decreased with increasing chain length and aquatic toxicity appeared to decrease with increasing chain length.

Table A-1. STEP 4: Matrix of Available and Adequate Data on Alpha-Olefin Category Members

Test	Hexene	Octene	Decene	Dodecene	Tetradecene
Physicochemical Properties					
Partition Coeff.	√	-	√	√	-
Water Solubility	-	-	-	-	√
Environmental Fate					
Biodegradation	√	-	√	√	√
Envir. Transport	-	-	-	-	-
Ecotoxicity					
Acute Fish	√	-	√	√	-
Acute Daphnid	√	-	√	√	-
Alga	√	-	√	√	-
Terrestrial	-	-	√	-	-
Human Health Effects					
Acute Oral	√	√	√	√	√
Acute Inhalation	√	√	√	√	√
Acute Dermal	√	√	√	√	√
Repeated Dose	√	√	-	-	-
Genotoxicity (in vitro -bacteria)	√	√	√	√	√
Genotoxicity (in vitro - non-bacterial)	√	√	-	√	√
Genotoxicity (in vivo)	√	-	-	-	-
Repro/Developmental	-	-	-	-	-

(√) = Data available and considered adequate; (-) = No data available, or available data considered inadequate.

Step 6: Prepare category test plan for public review. Table A-2 contains the proposed testing plan only for the endpoints for which new testing was recommended for the alpha-olefins. In this case it appears reasonable that if data gaps are filled by testing at the upper and lower ends of the homologous series (shaded regions in the table), and if the results suggest a pattern, then the remaining data gaps can be considered to fall within the ranges defined by the data.

Step 7: Conduct necessary testing. The shaded cells in Table A-2 show where new testing was recommended for the category.

Table A-2: Alpha-Olefin Proposed SIDS Test Plan[1]					
Selected SIDS Endpoint	**Hexene**	**Octene**	**Decene**	**Dodecene**	**Tetradecene**
Water Solubility	√/-	-	-	-	√/+
Acute Fish	√/+	-	√/+	√/+	-
Acute Daphnid	√/+	-	√/+	√/+	-
Acute Algae	√/+	-	√/+	√/+	-
Repeated Dose	√/+	√/+	-	-	-[2]
Repro/Developmental	-	-	-	-	-[2]

[1] KEY: √/- = data available, but not adequate; √/+ = data available and considered adequate; - = no data available. Shaded cells represent those SIDS endpoints for which testing was recommended.

[2] A combined repeated dose and reproductive/developmental toxicity screen study design was recommended.

Step 8: Evaluate new and existing data[4]. Table A-3 shows the results of the recommended testing and how it "fit" with available data for purposes of evaluating whether a pattern exists between some of the SIDS endpoints and the increase in 2-carbon increments from hexene to tetradecene. Note that there are four data points that exist in Table A-3 that were not present in Table A-2 (the octene water solubility and ecotoxicity results); these data were a late addition to the octene dossier and are included here to enhance the category analysis. This illustrates how all data should be considered in the evaluation of a category, even if it becomes available well after the literature search has been completed.

The new data show that patterns are clearly evident. For example, there is an apparent decrease in water solubility with increase in carbon chain length and a decrease in acute toxicity to fish and daphnids with an increase in carbon chain length. On the other hand, the mammalian toxicity data suggest a pattern of no difference between hexene and tetradecene for repeated dose (general) toxicity and developmental/reproductive toxicity.

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[4] The narrative presented in this section is an example of text that might appear in a "category analysis document" (see Figure 1 and main text). It should be noted that the new test data must still be submitted in the form of a robust summary.

Table A-3: Results of Alpha-olefin SIDS Category Testing[1]

Selected SIDS Endpoint	Hexene	Octene	Decene	Dodecene	Tetradecene
Water Solubility	50 mg/L[2]	(4.1 mg/L)[3]	-	-	0.0004 mg/L
Acute Fish	5.6 mg/L (LC_{50})	(4.8 mg/L)[3] (LC_{50})	>Water solubility? (Reported value >10,000 mg/L (LC_{50})	>Water solubility? (Reported value >1000 mg/L (LC_{50})	>Water solubility (LC_{50})
Acute Daphnid	10 mg/L (NOEC)	(3 < EC_{50} > 10)[3]	>Water solubility? (EC_{50})	>Water solubility? (EC_{50})	>Water solubility (LC_{50})
Acute Algae	>Water solubility (LC_{50})	(>Water solubility)[3] (LC_{50})	>Water solubility? (EC_{50})	>Water solubility? (EC_{50})	>Water solubility (LC_{50})
Repeated Dose	$NOEL_{oral}$ = 101 mg/kg (males) and >1000 mg/kg (females)	NOEL = 50 mg/kg (males)	-	-	$NOEL_{oral}$ = 100 mg/kg (males) and >1000 mg/kg (females)
Repro/ Developmental	$NOEL_{repro}$ and $NOEL_{dev}$ = >1000 mg/kg	-	-	-	$NOEL_{repro}$ and $NOEL_{dev}$ = >1000 mg/kg

[1] KEY: - = no data available; shaded cells represent those SIDS endpoints for which OECD recommended testing.

[2] Apparently this was the original value thought not adequate, but estimations of the water solubility were similar to this value, so a new study was not performed.

[3] These data were not identified as being available in the Testing Plan. However, because they were reported in the dossier, they are included here to enhance the category analysis.

Water solubility. The 50 mg/L value for hexene and 0.0004 mg/L value for tetradecene suggest a wide range of solubility for the five members of the group. The octene value of 4.1 mg/L suggests that the pattern (decreasing water solubility with increasing chain length) holds. Therefore, water solubility tests were judged not necessary and computer estimates (consistent with the latter premise for decene and dodecene) were considered acceptable.

Acute aquatic toxicity. The data in Table A-3 suggests that hexene and octene may exhibit moderate acute toxicity to fish and daphnids based on measured values (NOEC, LC_{50}, EC_{50}). However, all other members of the category appear to show no effects on fish and daphnids at saturation. In the case of algae, all category members show no effects at saturation. From a category perspective, it appears that a declining pattern exists for fish and daphnids (hexene and octene are more toxic than decene, dodecene, and tetradecene) but there was a flat pattern for algae (all members appeared equal). Based on this information, it was decided that no additional aquatic toxicity testing was necessary. The three literature values for octene noted in Table A-3 were considered acceptable. The aquatic acute toxicity for those endpoints correlate with water solubility, which in turn appear to determine (or limit) bioavailability of octene.

Repeated dose toxicity. The results presented in Table A-3 suggest that the general toxicity of hexene and tetradecene are similar, whereas octene appears more toxic than either hexene or tetradecene. In both cases, male rats were more sensitive to female rats. The effect observed in males, a male-rat specific kidney effect, does not appear to be relevant to humans. Also, both studies followed the OECD repeated

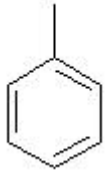
dose/reproductive/develop-mental toxicity screening testing protocol. There were no data for either decene or dodecene. The octene data point suggests that any category pattern that might exist (equal toxicity across all members) given the hexene and tetradecene data might not exist for the middle members of the category. However, upon closer inspection of the octene data in the octene dossier, it is seen that the doses used in the repeated-dose study were 5, 50, and 500 mg/kg. Since the LOEL was 500 mg/kg, the “true” NOEL is anywhere from 50 to 500. Therefore, given these data, it is reasonable to conclude that all members of the category likely have similar general toxicity under repeated dose conditions and testing of decene and dodecene is not required.

Reproductive/Developmental. The results presented in Table A-3 suggest that the general toxicity of hexene and tetradecene are similar, whereas octene appears more toxic than either hexene or tetradecene. In both cases, male rats were more sensitive than female rats. The effect observed in males, a male-rat specific kidney effect, does not appear to be relevant to humans. Also, both studies followed the OECD repeated dose/reproductive/developmental toxicity screening testing protocol. There were no data for either decene or dodecene. The octene data point suggests that any category pattern that might exist (equal toxicity across all members) given the hexene and tetradecene data might not exist for the middle members of the category. However, upon closer inspection of the octene data in the octene dossier, it is seen that the doses used in the repeated-dose study were 5, 50, and 500 mg/kg. Since the LOEL was 500 mg/kg, the "true" NOEL is anywhere from 50 to 500. Therefore, given these data, EPA would recommend that all members of the group likely have equal general toxicity under repeated dose conditions and testing of decene and dodecene is not required.

Example B: Linear Alkylbenzenes

Step 1: Identification of structure-based category: The linear alkylbenzene (LAB) category is comprised of nine different commercial formulations. Each formulation is a mixture containing various proportions individual LABs with the following formulae:

$$CH_3 - (CH_2)_x - CH - (CH_2)_y - CH_3$$



Where x + y = 7-13 and x = 0-7, giving a linear carbon range of C_{10} to C_{16}.

Thus, this category would fall under "family of mixtures" in terms of category type. Table B-1 presents the nine commercial products evaluated. Note that the LAB category may be further subdivided into three subcategories based on the percentage of alkyl substituents with a low (C_{10}-C_{11}), mid (C_{11}-C_{13}), and high (C_{13}-C_{14}) proportion of carbon chain lengths.

Table B-1: Assignment of LAB SubCategories[1]

LAB Formulation	Carbon Chain Length for Substituted Alkyl Group (Numbers represent percent of total)				
	C_{10}	C_{11}	C_{12}	C_{13}	C_{14}(2)
Nalkylene 500	21	39	31	7	<1
Nalkylene 500L	20	44	31	5	<1
Alkylate 215	16	43	40	1	<1
Nalkylene 550L	14	30	29	20	7
Alkylate 225	7	25	48	19	1
Nalkylene 575L	9	17	20	30	15
Nalkylene 600	<1	1	23	50	25
Nalkylene 600L	<1	1	23	50	25
Alkylate 230	1	2	16	50	30

1 The shaded regions create three subcategories by presenting two ends of the spectrum in terms of a higher proportion (>50%) of shorter carbon chains (upper left) and a higher proportion (>50%) of longer carbon chains (lower right). Bolded formulations had available data in all SIDS categories.
The proportion of C_{15} and C_{16} is < 1% in all formulations except for an incidence of 1% C_{15} in Alkylate 230.

Step 2: Gather published and unpublished literature for each member of the category. A literature search resulted in identifying data for most category members in the environmental fate, ecotoxicity and human health effect SIDS endpoints.

Step 3: Evaluate available data for adequacy. Again, as was discussed in the alpha-olefin example, evaluation of data adequacy is performed at the individual study level. Refer to the EPA guidance on Data Adequacy (*http://www.epa.gov/chemrtk/guidocs.htm*) for more information on this issue.

Step 4: Construct a matrix of SIDS endpoints indicating available/adequate data. An analysis of available data resulted in a matrix as presented in Table B-2. Again, for simplicity not all data found or compiled are presented here. Note that three LAB formulations (Alkylate 215, Alkylate 225, and Alkylate 230) had data available in each of the major SIDS classes (environmental fate, ecotoxicity, and health effects), and they each represent one of the three subcategories presented in Table B-1.

Table B-2. STEP 4: Matrix of Available and Adequate Data on LAB CategoryMembers[1]

LAB Formulation	Environ-mental Fate	Ecological Effects			Human Health Effects			
		Fish Acute	Daphnid Acute	Daphnid Chronic	Acute[4]	Repeated Dose[5]	Mutagen-icity[6]	Develop-mental[7]
Nalkylene 500	-				√	-		
Nalkylene 500L					-			
Alkylate 215	√	√	√	√	√	**-**	√	√
Nalkylene 550L	-				√	-		
Alkylate 225	√	√	√	-	√	√	√	**-**
Nalkylene 575L	-				-			
Nalkylene 600					√	-		
Nalkylene 600L					√			
Alkylate 230	√	√	√	√	√	√	√	√

[1] "√" denotes data are available and adequate. "-" denotes data are either not available, or are available and are judged inadequate. Shaded areas mark the three subcategories identified in Table B-1.

Step 5: Evaluate matrix data patterns. As with Table A-1 in the alpha-olefin example, the data in Table B-2 identifies where data gaps exist. Note that adequate data are available for most endpoints for the three LAB formulations mentioned above. Table B-3 is essentially the same table as Table B-2, except that the data values are placed in each cell so that they can be evaluated to determine the acceptability of the category approach for each endpoint.

Table B-3 shows a consistent pattern of no discernible difference in aerobic degradation among the three LAB formulations tested (range of 56% - 61% of parent material evolved as carbon dioxide after 35 day incubation period). Similarly, the acute fish toxicity, chronic daphnid toxicity, acute mammalian toxicity, reproductive/developmental toxicity, and mutagenicity data do not show differences across the tested formulations. However, the acute daphnid toxicity results, as well as the repeated dose toxicity tests in mammals suggest a pattern of increasing toxicity with an increase in the proportion of higher length carbon chains in the substituted alkyl group that appears to hold for each of these SIDS endpoints.

Step 6, 7, and 8: Prepare category test plan for public review; Conduct necessary testing; and Evaluate new and existing data. In this case, it was concluded that no further testing was necessary under the SIDS program and that the existing data were sufficient for a screening level hazard assessment. Thus; it was not deemed necessary to test each LAB formulation given the results of testing in three separate formulations to represent the boundaries of the category.

In this example, the test plan would include both the rationale for "no testing" and the category analysis narrative interpreting the existing data. Robust summaries for the individual supporting studies would also be available.

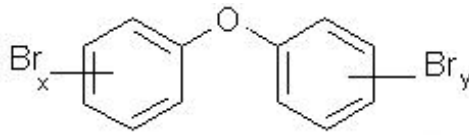
Table B-3: Evaluation of Matrix Data Patterns for LAB Category

LAB Formulation	Environmental Fate	Ecological Effects			Human Health Effects			
		Fish Acute	Daphnid Acute	Daphnid Chronic	Acute[4]	Repeated Dose[5]	Mutagen-icity[6]	Develop-mental[7]
Nalkylene 500	Not tested	Not tested			>34 g/kg	Not tested		
Nalkylene 500L					Not tested			
Alkylate 215	**56%[1]**	**> Water solubility**	**80 ppb[2]**	**7.5 to 15 ppb[3]**	**17 g/kg**	**100 mg/m^3**	**Negative**	**125 mg/kg**
Nalkylene 550L	Not tested	Not tested			>5 g/kg	Not tested		
Alkylate 225	**61%[1]**	**> Water solubility**	**9 ppb[2]**	**Not tested**	**28 g/kg**	**29 mg/m^3**	**Negative**	**Not tested**
Nalkylene 575L	Not tested	Not tested			Not tested			
Nalkylene 600	Not tested	Not tested			>35 g/kg	Not tested		
Nalkylene 600L					>5 g/kg			
Alkylate 230	**56%[1]**	**> Water solubility**	**10 ppb[2]**	**13 to 23 ppb[3]**	**21 g/kg**	**<32 mg/m^3**	**Negative**	**125 mg/kg**

[1] Percent of parent material evolved as carbon dioxide after 35 days in an aerobic biodegradation test.
[2] 48-hour LC_{50}s.
[3] 21-Day No Observed Effect Concentration (NOEC).
[4] Oral LD_{50}s in rodents.
[5] Four week inhalation studies in rats, values represent NOECs for the following effects: irritation of the eyes and nose and decreased body weight.
[6] Negative in in vitro (bacteria - Ames; mammalian - Chinese hamster ovary cells) and in vivo (chromosomal aberration study in rats) tests.
[7] Developmental toxicity study (oral, rats, doses of 0, 125, 500, and 2000 mg/kg/d). Numbers in column represent no observed adverse effect level (NOAEL) for both maternal (weight gain) and developmental (ossification variations) endpoints.

Example C: Brominated Diphenyl Ethers

Step 1: Identification of structure-based category. The brominated diphenyl ether (BDE) category contains three chemicals: bis (pentabromophenyl) ether, or decabromodiphenyl, ether; diphenyl ether, octabromo derivative; and diphenyl ether, pentabromo derivative. The general chemical formula for this category is:



x + y = 5, 8, 10

This category would fall under the "family of congeners" category type. This particular example is limited to an analysis of ecotoxicity data. The human health data were handled for each chemical separately, instead of as a category, in the SIDS program.

Step 2: Gather published and unpublished literature for each member of the category. A literature search resulted in identifying some ecotoxicity data for most category members.

Step 3: Evaluate available data for adequacy. As with the other examples in this Appendix, evaluation of data adequacy is performed at the individual study level. Refer to the EPA guidance on Data Adequacy (*http://www.epa.gov/chemrtk/guidocs.htm*) for more information on this issue.

Step 4: Construct a matrix of SIDS endpoints indicating available/adequate data. Table C-1 lists the available ecotoxicity based on the literature search. SIDS data gaps exist for acute invertebrate testing (decabromodiphenyl ether) and for acute algae testing (octabromodiphenyl ether).

Table C-1. STEP 4: Available Acute Ecotoxicity Data on BDEs[1]

Test Organism	Penta BDE	Octa BDE	Deca BDE
Fish	√	√	√
Invertebrate	√	√	-
Algae	√	-	√

[1] "√" denotes data available and adequate; "-" denotes data not available, or available and not adequate.

Step 5: Evaluate matrix data patterns. Table C-2 is essentially the same table as Table C-1, except that actual data replace the "√s".

In evaluating these data, it was concluded that there would likely be a decrease in aquatic toxicity as you increase the number of bromines within the BDE category. Since there were adequate aquatic toxicity data for the category member with the lowest number of bromines (pentaBDE), it would not be necessary to conduct additional acute toxicity tests on the remaining members which had a higher number of bromine atoms.

In addition to the ecotoxicity data, available data on environmental monitoring, bioconcentration, and the physico-chemical properties of the category members were evaluated. It was determined that there was a decreasing concern for bioaccumulation potential with an increase in bromine number; that all three compounds were not very water soluble; and that they all had high log K_{ow}s. This suggested that the likely exposure scenario of concern would be to organisms exposed directly to sediment or soil.

Table C-2: Available Acute Ecotoxicity Data on BDEs

Test Organism	Penta BDE	Octa BDE	Deca BDE
Fish	Rainbow trout NOEC (96 hr) = 21 ug/L (>water solubility?)	Medaka LC_{50} (48 hr) = >water solubility	Medaka LC_{50} (48 hr) = >water solubility
	Medaka LC_{50} (48 hr) = > water solubility		
Invertebrate	Daphnid EC_{50} (48 hr) = 14 ug/L NOEC (48 hr) = 4.9 ug/L (both values > water solubility)	Daphnid 21-day NOEC > 2 ug/L	No Data
Algae	*Selanastrum capricornutum* NOEC (96 hr) up to 26 ug/L (>water solubility?)	No Data	Three different species EC_{50} (72 hr) > water solubility

Step 6: Prepare category test plan for public review. Because of the concern for bioaccumulation and partitioning of the BDEs to the sediment/soil environment, it was recommended that further testing (chronic aquatic toxicity, sediment toxicity, and earthworm toxicity) be conducted, however, this testing should begin with pentaBDE. Therefore, the final testing recommendation required "advanced" SIDS testing without filling the acute aquatic toxicity basic SIDS data gaps. The testing plan (Table C-3) was approved to follow a tiered fashion; the results of the lower tiers determining the next set of tests.

Table C-3: OECD SIDS Proposed Ecotoxicity Testing Plan with BDEs

Tier	Category Member	Ecotoxicity Test[1]	Comment
I	PentaBDE	Daphnid reproduction Fish early life stage test	Daphnid study to verify that acute effects were due to toxicity. Fish test to verify bioaccumulative potential.
		Sediment (invertebrate) and soil (earthworm, plant, nitrification) toxicity tests	To verify concerns identified in hazard assessment
II	OctaBDE	Sediment and soil toxicity	Depends on results of pentaBDE
III	DecaBDE	Sediment and soil toxicity	Depends on results of octaBDE

[1] All tests are beyond the basic SIDS requirements. The testing plan is presented to show how basic SIDS requirements were waived in order to proceed to a more meaningful testing scheme.

Step 7: Conduct necessary testing. The proposed testing plan has not yet been implemented.

Step 8: Evaluate new and existing data. SIDS case has not yet progressed to this step.

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URL: http://www.epa.gov/opptintr/chemrtk/catdoc29.htm