Step 7. Conduct necessary testing.

34. The results of the testing plan are summarised in Table C-4.

Step 8. Perform an external assessment of the category.

35. The Tier I testing was carried out using pentaBDE alone and consisted of long-term toxicity tests with exposure via water (tests with daphnids and rainbow trout), sediment (tests with midges, oligochaetes and amphipods) and soil (tests with earthworms, plants and soil microorganisms). The results of these tests verified concerns over the toxicity of the substance to fish and daphnids over long-term exposures, and confirmed that the substance could also elicit toxic effects on sediment- and soil-dwelling organisms. The Tier II (octaBDE) and Tier III (decaBDE) testing was actually performed in parallel, based on the most sensitive soil and sediment organisms identified in the Tier I testing.

36. In addition to the prescribed test plan, new information also became available on the accumulation potential of one member of the category, namely decaBDE. This showed that decaBDE was present in certain predatory birds and their eggs, as well as certain terrestrial mammals. Before these data were available it was assumed that decaBDE had a very limited potential for uptake and accumulation in organisms because of its large molecular size and low fish bioconcentration factor. In addition, new data also became available that appeared to show that the substance may cause neurotoxic effects in young laboratory mice at doses much lower than those causing effects for other toxicity endpoints (although further testing is currently underway to confirm this effect and establish a NOAEL). These new data required the assumptions over the low accumulation and hazard potential of decaBDE to be re-evaluated.

Step 9: Fill the data gaps

37 A major problem encountered with this category was that two members (octa- and decaBDE) showed effectively no toxicity in any of the aquatic (water exposure), sediment or soil toxicity tests undertaken. For aquatic toxicity it was possible to read-across between the various members of the category to fill the data gaps once the further testing for pentaBDE was completed, as follows. All three category members showed essentially no toxicity to fish from acute exposures. Penta- and decaBDE showed essentially no toxicity to algae, and so it was possible to infer that octaBDE would also show essentially no toxicity to algae. The long-term toxicity data for pentaBDE showed that invertebrates were the most sensitive trophic level. As octaBDE had no effect on daphnids following long-term exposure at concentrations up to its solubility limit, it was also possible to infer that decaBDE would show no effects with daphnids. Furthermore, both octa- and decaBDE were also considered unlikely to show any long-term effects in fish tests at concentrations up to their respective solubility limits (since both have a lower fish bioconcentration factor than pentaBDE).

38. In retrospect, it would have been possible to read-across from the octaBDE data to predict that decaBDE would also show little or no toxicity to soil and sediment organisms. However, at the time it was not possible to carry out this read-across with any certainty; regulatory experience with these types of tests is less extensive than for aquatic tests (for industrial chemicals), and the possible exposure in sediment and soil is not necessarily limited by the water solubility of the substances (oral exposure could be important). There was also a policy need to complete the testing as quickly as possible, and so the testing on both octaBDE and decaBDE was performed at the same time.

39. It should be noted that the main driver for the further testing requirements of octa- and decaBDE was consideration of the main compartments through which organisms may be exposed (i.e. sediment and soil) rather than to complete the SIDS endpoints (mainly related to exposure through water).

40. Overall, read-across of data was compromised by the fact that two members out of three essentially showed no toxicity in standard tests. The number of members in the category is an important consideration because it is very difficult to reliably identify trends from two data points (for example, it would generally not be possible to predict the behaviour of pentaBDE from that of octa- or decaBDE). The patterns and trends in the data for this category only really became evident once a substantial amount of testing had been carried out. However, it was useful to identify the most sensitive species in tests with the most toxic member of the category, which could then be used to target the testing for the other members of the category.

41. Another problem encountered with this category was that, with the exception of decaBDE, the commercially supplied substances contain a mixture of congeners. Much of the available ecotoxicity information was obtained with these commercial products and these data did not allow the actual toxicity of the individual congeners to be ascertained, except for the broad trends. This contrasts with the situation regarding the data on the environmental exposure of this group of substances, where a large database of monitoring data relating to specific isomers is available.

42. Perhaps most importantly for this category, it was not possible to identify or infer the particular accumulative properties of decaBDE using a read-across approach. For example, the available laboratory studies show that pentaBDE has a much higher accumulation potential than decaBDE and this is also demonstrated by the majority of the available environmental monitoring data (particularly for the aquatic environment). However, it has recently become apparent that decaBDE can be widely found in certain predatory birds and their eggs and some predatory mammals, possibly linked to the terrestrial food chain. This finding means that it is necessary to re-visit the category assumptions when new information on a category member is made available.

Example D: Butene Isomers and their Mixtures

Step 1: Define the category

43. An example of a category of isomeric substances and their mixtures is the butenes. This category includes four isomers (two structural isomers, butene-1 and isobutene), two geometric isomers, *cis*-butene-2 and *trans*-butene-2 and two mixtures (see table D-1) Substance structures are shown in Figures D-1 to D-4.

Figure D-1. Molecular Structure of Butene-1 (C4H8)

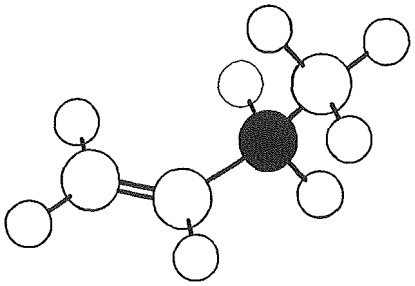


Figure D-2. Molecular Structure of Isobutene (2-methyl propene) (C4H8)

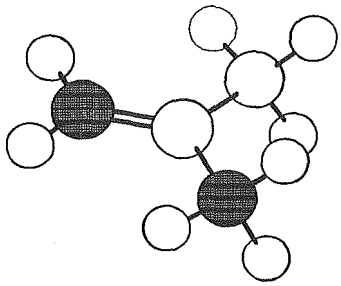


Figure D-3. Molecular Structure of *cis*-Butene-2 (C4H8)

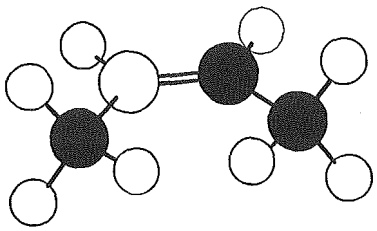
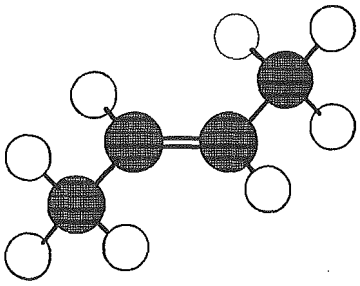


Figure D-4. Molecular Structure of *trans*-Butene-2 (C4H8)



44. Each butene isomer contains four carbon and eight hydrogen atoms, with one double bond between carbon number one and two or carbon number two and three. These are simple hydrocarbons in a class referred to as alkenes. At standard temperature and pressure (STP), they are gaseous.

45. Butenes are a good example of an isomer category because their physicochemical and biological properties are closely aligned. Based on existing data for toxicological endpoints within the HPV Chemicals Programme and the overall toxicological knowledge of hydrocarbons, the Butenes Category members that do not have toxicological data would be expected to exhibit similar if not identical effects as category members with data (the toxicological endpoints under consideration include mammalian and environmental as specified under the Programme). Additionally, because of their similarity with respect to physicochemical and biological parameters, data on the individual substances can be used to estimate values for the mixtures.

46. It should be noted that the Butenes Category example is relatively simple with a limited number of isomers. As the number of carbon atoms and functional moieties increase, the number of isomers increases illustrating the importance of appropriately defining isomer categories when optimising the use of existing data.

Step 2: Gather published and unpublished data for each category member

47. A comprehensive literature search identified information on all SIDS endpoints for the category members. The majority of information was found on the single isomers rather than on the mixed isomers. Participating companies in the consortium were asked to review their internal files for appropriate information.

Step 3: Evaluate available data for adequacy

48. Each study identified by the literature search was reviewed and assessed for quality and reliability (section 3.1). Data were entered into IUCLID 4.01 under the specific CAS number for each the isomers or as mixture as part of a "Butenes Isomers and their mixtures", category record. Those studies that were considered appropriate were classified as "Critical study for SIDS Endpoint". For several health related endpoints, more than one "critical study" was identified.

Step 4: Construct a matrix of data availability

49. The IUCLID category matrix report was used to automatically generate tables containing substance identity, end point, data availability and their values. The table is not reproduced here to save space, but a summary is given in Table D-1.

TABLE D-1

Matrix of available and adequate data on butenes: isomers and their mixtures						
Test	***1-Butene***	***Butene, mixed -1 and -2- isomers***	***2-Methylpropene***	***Butene, mixed isomers***	***cis-2-Butene***	***trans-2-Butene***
	106-98-9	107-01-7	115-11-7	25167-67-3	590-18-1	624-64-6
Physicochemical Properties						
Melting Point	√	–	√	–	√	√
Vapour Pressure	√	–	√	–	√	√
Partition Coeff.	√	–	√	–	√	√
Water Solubility	√	–	√	–	√	√
Environmental Fate						
Biodegradation	–	–	–	–	–	–
Ecotoxicity						
Acute Fish	√	–	√	–	√	√
Acute Daphnid	√	–	√	–	√	√
Alga	√	–	–	–	√	√
Terrestrial	√	–	√	–	√	√

Human Health Effects						
Acute Oral	-	-	-	-	-	-
Acute Inhalation	-	√	√	-	-	-
Acute Dermal	-	-	-	-	-	-
Repeated Dose	√	√	√	-	-	-
Genotoxicity (*in vitro*)	√	√	√	-	-	-
Genotoxicity (*in vitro* - non-bacterial)	-	√	√	-	-	-
Genotoxicity (*in vivo*)	√	-	√	-	-	-
Repro/Developmental	√	√	-	-	-	-
(√) = Data available and considered adequate; (-) = No data available, or available data considered inadequate.						

50. As butenes are gaseous at STP the data for environmental toxicity are calculated values, using the ECOSAR program. Human health data are available for all endpoints, with a minimum of two category members having reliable data.

Step 5: Perform an internal assessment of the category

51. The information in Table D-1 was assessed for trends. For environmental toxicity data, values were calculated for each endpoint. These values were similar for each member, and are therefore considered to be applicable to the mixed isomer category members, for which it is not possible to calculate values.

52. For the health endpoints, where there were data, they were similar for all category members within the considerations of study variability. Table D-2 shows selected data from the IUCLID category report.

TABLE D-2

Endpoint	*Substances*					
	1-Butene	***Butene, mixed -1 and -2- isomers***	***2-Methylpropene***	***Butene, mixed isomers***	***cis-2-Butene***	***trans-2-Butene***
	106-98-9	107-01-7	115-11-7	25167-67-3	590-18-1	624-64-6
Acute Inhalation Toxicity		LC50: male/female rat > 10057 ppm for 4 hour(s)	* LC50: rat = 620 mg/l (270000ppm) for 4 hour(s)			
Repeated Dose Toxicity	Male/female rat; other: vapour inhalation; 28 days; 6 hours/day, 7 days/week; Doses: 0, 500, 2000 and 8000 ppm; Method: OECD combined study	Male/female rat; inhalation; 2 weeks NOAEL: = 2500 ppm	Male/female rat; inhalation; 13 weeks NOAEL: 8000 ppm *			

	TG422; NOAEL: = 8000 ppm					
Genetic Toxicity *in vitro*	* Salmonella negative	* Salmonella negative	* Mouse lymphoma L5178Y TK+TK- negative			
Genetic Toxicity *in vivo*	Mammalian Bone Marrow Erythrocyte Micronucleus Test Negative		Micronucleus assay mouse negative			
Toxicity to Reproduction	OECD Guide-line 422 parental NOAEL = 8000 ppm	OECD 422 NOAEL Maternal toxicity: = 2500 ppm; NOAEL Teratogenicity: 5000 ppm				
Developmental Toxicity / Teratogenicity	OECD Guide-line 422 NOAEL parental: = 2500 ppm; F1: >= 5000 ppm		OECD 414 NOAEL Maternal toxicity: > 8000 ppm; NOAEL Teratogenicity: > 8000 ppm			

* Endpoint where there was more than one study identified as a "critical" study. For the sake of this illustration only one study is shown. Multiple Endpoint data were not conflicting with data shown.

Step 6: Prepare category test plan

53. No testing was proposed.

Step 7: Conduct the necessary testing

54. No testing was proposed.

Step 8: Perform an external assessment of the category

55. No new information was generated so this step was not performed.

Step 9: Fill data gaps by read-across, extrapolation, interpolation etc

56. Read-across techniques can be applied to pure isomers within a category. For example, the log octanol-water partition coefficient (log P_{ow}) of *cis*-butene-2 is 2.3. If log P_{ow} data were not available for trans-butene-2, based on the structural similarity, the data for *cis*-butene-2 could be used to estimate the log P_{ow} of trans-butene-2, e.g. log P_{ow} =2.3. Selected properties of the pure isomers can also be used to characterise a mixture containing the isomers. Using butene isomer log P_{ow} data as an example, if only

butene-1 and isobutene data were available, 2.4 and 2.3, respectively, those data could be used to characterise the log P_{ow} of a substance containing all the butene isomers. The log P_{ow} value for such a substance could be represented as 2.3 to 2.4.

57. Although the previous discussion focused on a physicochemical endpoint, extrapolation of environmental and mammalian toxicity data are also possible from category members with data to those without data. It was possible to calculate select acute aquatic toxicity endpoints, including those within the Programme. However, if that had not been possible, the acute fish toxicity data for *cis*-butene-2 could have been used to estimate the toxicity of trans-butene-2. The appropriateness of this read-across would be justified based on the knowledge that the mode of toxic action for hydrocarbons is non-polar narcosis and that the toxic mechanism is disruption of biological membrane function. Therefore, because these substances would exert a similar biological effect and they would be expected to do so over a relatively narrow range. Based on their similar log P_{ow} values, an effect value (i.e., 96-hour fish LC50) for one butene isomer could be used to estimate the toxicity of another (the calculated fish toxicity values for the butene isomers range from 17 to 21 mg/L). Equally, if acute fish toxicity data were available for *cis*-butene-2, those data could be used to characterise the toxicity of a substance that contained *cis*-butene-2 and *trans*-butene-2.

58. An example of read-across as it can be applied to human health endpoints includes the application of repeated dose toxicity studies for three of the substances in this category (butene-1, isobutene, and butene mixed -1 and -2 isomers) to characterise the three substances without data (*cis*-butene-2, *trans*-butene-2, and butene mixed isomers). The three substances with data clearly indicate that they have a low order of subchronic toxicity. Adaptive and reversible changes in the liver indicate butenes were widely distributed within the body and metabolised. No Observed Adverse Effect Levels (NOAEL) from studies for tested members over 28-days to 2 years range from 2,000 ppm to 8,000 ppm. By read-across, the untested butene substances would also be expected to demonstrate a low order of subchronic toxicity over the extent and within the range to which the tested butenes were subjected, or to the lowest concentration of the range at a minimum.

59. Members of the Butenes Category that have been tested do not produce mutagenic responses either in *in vitro* or *in vivo* test systems. Butene-1, butene 1 and 2 mixed isomers, and isobutylene did not induce gene mutations in reverse mutation assays conducted in S. typhimurium and/or E. coli either in the presence or absence of metabolic activation. Butene-2 was not clastogenic to rat lymphocytes *in vitro*. Isobutylene tested negative in an *in vitro* cell transformation assay using a mouse embryo fibroblast derived cell line and in a mouse lymphoma assay both in the presence or absence of metabolic activation. In addition, neither 1-butene nor isobutylene induced micronuclei formation in mouse bone marrow cells. By read-across, these data support characterising the untested members of the Butenes Category as also having a low potential for carcinogenicity.

60. Inhalation reproductive/developmental toxicity studies conducted with butene-1, butene-2 mixed isomers, and isobutylene resulted in a NOAEL for each study that was the highest exposure concentration tested (5,000 to 8,000 ppm). Based on the weight of the experimental evidence and the consistent absence of observed significant toxic findings, the untested members of the Butenes Category would be expected to have a low potential for chronic, reproductive, and/or developmental toxicity and cancer.

61. Supportive evidence to consider the butenes as a category for mammalian toxicity endpoints is provided by an understanding of metabolism for selected butenes and their mode of action. Additionally, physicochemical data add to an overall understanding of the potential for distribution and data confirm that isomer form does not change toxicity. Metabolism of isobutylene via cytochrome P450 to an epoxide, 2-methyl-1,2-epoxypropane (MEP), has been demonstrated, and MEP has been identified as the primary metabolite in liver tissue of various species, including man. Epoxidation of *cis*- and *trans*-butene-2 has also

been demonstrated. It is known that inhalation of these substances, only at very high concentrations, can produce central nervous system depression, anaesthesia and/or asphyxiation. For example, isobutylene is predicted to produce narcosis in man at concentrations exceeding the lower explosion limit of 18,000 ppm. Other butene substances would therefore also be expected to exhibit a similar low order of acute toxicity. Both the log P_{ow} and water solubility favour absorption via the lung and their small molecular weight and log P_{ow} suggest that butenes are likely to be widely distributed within the body. From data on tested butenes, it can be concluded that branching does not affect the toxicity of butenes. Evaluation of this information provides further support beyond the base toxicity data that butene substances would behave similarly in mammalian systems and exert similar degrees or lack of effects.

Example E : HYDROCARBON SOLVENTS

[Note: The categories for Hydrocarbon Solvents have not been assessed by SIAM yet. The description below is based on the preparatory work of the sponsor organisations (International Hydrocarbon Solvents Consortium and US-EPA), as well as the discussions held at the OECD workshop on the development and use of chemical categories held in January 2004. The descriptions below might have to be revised once the categories have undergone assessment at SIAM.]

Background

62. Hydrocarbon solvents assessed under the OECD HPV Chemicals Programme include aliphatic hydrocarbon solvents in the C5-C20 range and aromatic hydrocarbon solvents in the C9-C12 range. Production of hydrocarbon solvents is differentiated from other refinery substances such as gasoline and diesel fuel by additional processing steps leading to finished substances with narrow distillation range, a defined aromatic content, removal of benzene, polyaromatic hydrocarbons (PAHs), sulfur- and nitrogen-containing compounds, and low color. These additional refining steps are necessary in order to make substances with qualities suitable for consumer applications. The specific isomer content of most hydrocarbon solvents is not specified as these products are complex substances, not preparations or intentional mixtures, and may contain dozens or even hundreds of individual isomers. However, these substances are well characterized for their general chemical composition in terms of their paraffin, cycloparaffin, and aromatic content. In addition, the composition of specific constituents of concern (e.g., n-hexane, naphthalene) is well defined.

Aliphatic Hydrocarbon Solvents

63. Aliphatic hydrocarbons consist of carbon and hydrogen molecules arranged as straight chain (n-paraffins or n-alkanes), branched chain (isoparaffins), or cyclic hydrocarbons (naphthenes). They contain no reactive functional groups (e.g., alkenes, sulfides, alcohols, etc.). Commercial aliphatic hydrocarbon solvents can be individual hydrocarbons (e.g., n-pentane) or multi-constituent combinations of aliphatic hydrocarbons. These multi-constituent hydrocarbon solvents include products that are composed of one type of hydrocarbon chemistry (e.g., isoparaffins) or multiple types (e.g., white spirits, Varnish Makers and Painters (VM&P) Naphtha). Multi-constituent hydrocarbon solvents are primarily defined by distillation range and flash point. In addition, aliphatic hydrocarbon solvents are also be defined by the amount of aromatic compounds they contain. The petroleum feedstocks used to make many aliphatic hydrocarbon solvents contains some aromatic hydrocarbons (normally less than 23%). For some aliphatic hydrocarbon solvents, such as regular mineral spirits or white spirits, these aromatic hydrocarbons are purposely retained in the final product to achieve or enhance certain solvency properties. The term dearomatized refers to those products that have undergone an additional step to remove or hydrogenate the aromatic compounds contained in the feedstock (e.g., dearomatized mineral spirits), resulting in an aliphatic hydrocarbon solvent with little or no aromatic content (≤2%). Some aliphatic hydrocarbon solvents, such as isoparaffins or n-paraffins, are produced through a polymerization process that involves the hydrogenation of an olefin (e.g. ethylene, propylene) oligimerization product. Petrochemicals produced in this manner are commonly referred to as synthetics because they are synthesized from smaller molecules rather than being derived from petroleum streams.

Aromatic Hydrocarbon Solvents

64. Aromatic hydrocarbons in the C9-C12 range are either one aromatic-ring structures with alkyl side chains (alkylbenzenes) or two aromatic-ring structures with alkyl side chains (alkylnaphthalenes). C9 aromatic hydrocarbon solvents contain isomers of trimethylbenzene, isomers of ethyltoluene, cumene (isopropylbenzene), n-propylbenzene and small amounts C8 and C10 aromatic hydrocarbons. Aliphatic

hydrocarbons of similar molecular weight may also be present in very small amounts, generally <1%. These products contain only traces of benzene (<10 ppm) and toluene (<100 ppm). Aromatic hydrocarbon solvents in the C10-C12 range contain isomers of alkylbenzenes and alkylnaphthalenes; some contain up to 10% naphthalene.

Step 1: Identify structure-based category and its members.

Hydrocarbon Solvent Categories

65. Nine categories were identified to address the different types of commercial hydrocarbon solvents in the C5-C20 range. These categories are listed below and each category is addressed in separate test plans.

C5 Aliphatic Hydrocarbon Solvents
C6 Aliphatic Hydrocarbon Solvents
C7-C9 Aliphatic Hydrocarbon Solvents
C9-C13 Aliphatic [≤2% Aromatics] Hydrocarbon Solvents
C9-C13 Aliphatic [2-23% Aromatics] Hydrocarbon Solvents
C14-C20 Aliphatic [≤2% Aromatics] Hydrocarbon Solvents
C14-C20 Aliphatic [2-35% Aromatics] Hydrocarbon Solvents
C9 Aromatics Hydrocarbon Solvents
C10-C12 Aromatics Hydrocarbon Solvents

66. There are many different hydrocarbon solvent substances within the C5-C20 range being addressed. While there may be several potential ways to categorize and review these substances, the above categories appear to be the best way of organizing the substances based on physical-chemical properties (e.g. vapor pressure), commercial applications, uses, and toxicity. In developing these categories, it was intended that similar commercial products, with similar applications, be in the same category. Substances with similar hydrocarbon structures (e.g., aromatic) would be placed in the same category. Finally, special consideration was given to previously reviewed substances. For example, a separate category was developed for C9 Aromatic Hydrocarbon Solvents because the of U.S. EPA Toxic Substances Control Act (TSCA) C9 Test Rule on C9 aromatics (ethyltoluene and trimethylbenzene isomers).

Underlying Hypothesis for the Formation of the Categories

67. There are essentially two key underlying hypotheses for the formation of the hydrocarbon solvent categories. The first is that hydrocarbon solvents can be grouped around major product types (e.g., hexanes, VM&P Naphtha, Mineral Spirits/White Spirits, etc.). Because there are so many different commercial and trade names used for hydrocarbon solvents, it was decided that generic names (e.g., C7-C9 Aliphatic Hydrocarbon Solvents) would be the most appropriate for the OECD HPV Chemicals Programme. While commercial hydrocarbon solvent products are frequently defined by distillation range, it was felt that grouping hydrocarbon solvents by predominant carbon number range would be easier and more practical than grouping the hydrocarbon solvents by boiling range because of simpler nomenclature, easier identification, and selection of representative constituents for modelling. The second hypothesis for the formation of the categories is that aliphatic isomers within a particular carbon range, regardless of them being straight-chained, branched, or cyclic, and aromatic hydrocarbons within a particular carbon range have similar physicochemical, environmental fate, and toxicological properties. The two defining toxicological characteristics of hydrocarbon solvents are central nervous system depression and upper respiratory tract irritation observed at high airborne concentrations. The hypothesis that these two toxicity endpoints are related to and can be predicted by carbon chain length and aromatic content is supported by reviews appearing in various standard toxicology texts, including Patty's Industrial Hygiene and

Toxicology, Browning's Toxicology of Industrial Solvents, and Caserett and Doulls Toxicology. The single well-known exception is n-hexane, which produces a specific type of axonapathy resulting from metabolism to the gamma diketone 2,5-hexanedione. The specific structural requirement for the axononapthy induced by gamma diketones is also described in standard toxicology texts.

Technical and Practical Issues in Forming the Categories

68. The grouping of hydrocarbon solvents was proposed around hydrocarbon chemistry (e.g. isoparaffins, n-paraffins, alkylbenzenes) and major product types (C9-C13 Multi-constituent Hydrocarbon Solvents). There are a number of important technical issues when evaluating complex substances. One is that environmental fate and physicochemical data cannot be modelled for complex substances. To address this issue, representative constituents were identified for each category to cover the carbon range and hydrocarbon structures of the category. These constituents were then modelled for the SIDS environmental fate and physicochemical endpoints. Measured data on the commercial products is available for most of the physicochemical endpoints, so this is also provided. Generally the modelled constituent data and measured whole product showed good correlation, further supporting the categories. Major usage categories were also a practical consideration in forming the categories.

As an example, Table E.1 presents the proposed category for C7-C9 Aliphatic Hydrocarbon Solvents.

Table E.1: Substances in the C7-C9 Aliphatic Hydrocarbon Solvents Category

Class/Dossier	CASRN	Chemical Name
Normal Paraffins	142-82-5	Heptane
	111-65-9	Octane
	111-84-2	Nonane
Isoparaffins	70024-92-9	Alkanes, C7-8-iso-
	90622-56-3	Alkanes, C7-10-iso-
Multi-constituent C7-C9 Aliphatics	8032-32-4	Ligroine
	64741-63-5	Naphtha, (petroleum), light catalytic reformed
	64741-84-0	Naphtha, (petroleum), solvent-refined light
	64742-48-9	Naphtha, (petroleum), hydrotreated heavy
	64742-49-0	Naphtha, (petroleum), hydrotreated light
	64742-89-8	Solvent naphtha, (petroleum), light aliph.
	92045-53-9	Naphtha (petroleum), hydrodesulf. light, dearoma.
	426260-76-6	Heptane, branched, cyclic and linear

Step 2: Gather published and unpublished data for each category member.
Step 3: Evaluate available data for adequacy
Step 4: Construct a matrix of data availability (SIDS endpoints vs. category members) and indicate in the cells of the matrix whether existing data are available.

69. These three steps were essentially done almost in parallel once the categories were formed. Available data from company proprietary files, the peer-reviewed literature, and modelled data for environmental fate and physicochemical endpoints were collected, placed in a matrix and evaluated. Data were evaluated for study reliability in accordance with the OECD guidance. Only studies which met the reliability criteria of "1" (valid without restriction) or "2" (valid with restrictions) were included in this review. In a few cases, additional data for substances with the same CAS RN exist in the ECB (European Chemicals Bureau) IUCLID (International Uniform Chemical Information Dataset). These data were evaluated and included in the review only if it was determined that the substances were compositionally relevant and met the reliability criteria of "1" or "2." After these data evaluations were complete, the any necessary testing to fill data gaps was proposed. Preliminary recommended changes from EPA on the test plans included the proposed addition of chronic aquatic toxicity data for categories with a log Kow above 4.2. Table E.2 and E.3 provide the matrices for the C7-C9 Aliphatic Hydrocarbon Solvents Category.

Table E.2 C7-C9 Aliphatic Hydrocarbon Solvents Category – Toxicity Endpoints Matrix

Endpoints	Multi-Constituent Substances (i-,n-,cy-)	Isoparaffins	Normal Paraffins
Acute	1[1] - Low	- Low	- Low
Assigned Value[2]	**Low**	**Low**	**Low**
Repeat-Dose	- No Target Organ	- No Target Organ	- CNS/No Target Organ
Assigned Value	**No target organ effects; CNS at high conc.**	**No target organ effects; CNS at high conc.**	**No target organ effects; CNS at high conc.**
Genetic – *in vitro*	-Negative (bac.) -Negative (mam.)	-Negative (bac.) -Negative (mam.)	-Negative (bac.) Read-Across (mam.)
Assigned Value	**Negative**	**Negative**	**Negative**
Genetic – *in vivo*	-Negative (new testing)	-Negative	Read-Across
Assigned Value	**Negative**	**Negative**	**Negative**
Reproductive	- No Repro Effects	Read-Across	Read-Across
Assigned Value	**No Repro Effects**	**No Repro Effects**	**? – Under Discussion**
Developmental	- No Develop Effects	- No Develop Effects	Read-Across
Assigned Value	**No Develop Effects**	**No Develop Effects**	**No Develop Effects (?)**

[1] - Study Available.
[2] Assigned Value – Given available data, information, and construct of category, the value assigned to cells for which there are no data.

Table E.3 C7-C9 Aliphatic Hydrocarbon Solvents Category – Aquatic Endpoints Matrix

Endpoints	Multi-Constituent Substances (i-, n-, cy-)	Isoparaffins	Normal Paraffins
Acute Fish	D[1] – Moderate	Read-across	D - Moderate
Assigned Value[2]	Moderate	Moderate	Moderate
Acute Invertebrate	D - Moderate	Read-across	D - Moderate
Assigned Value	Moderate	Moderate	Moderate
Algae Toxicity	D - Moderate	Read-across	Read-across
Assigned Value	Moderate	Moderate	Moderate
Chronic Invertebrate	D (Test Underway)	Read-across	Read-across
Assigned Value			

[1] D - Study available
[2] Assigned Value – Given available data, information, and construct of category, the value assigned to cells for which there are no data.

Use of Read-Across Data

70. The categories were initially developed around commercial hydrocarbon solvents. The available data were then reviewed and the categories were evaluated based on this data; in some case the categories were reorganized. As these product categories are in sequence and data are available at a number of points across the spectrum of hydrocarbon solvents, use of read-across data was considered in some cases. Use of read across is limited to chemicals of very similar structure. For example, in the C7-C9 Aliphatic Hydrocarbon Solvents category data for C7-C9 normal paraffins, C7-C9 isoparaffins, and complex C7-C9 multi-constituent aliphatic substances (products containing normal, iso-, and cycloparaffins) were used to read across (either quantitatively or qualitatively) to cover all the substances in the category. Where data were not available and read-across could not be justified, additional testing was proposed.

Step 5: Evaluate the category approach.

71. Since most of the SIDS endpoint data for hydrocarbon solvents were already available, the verification of the two key category hypotheses generally occurred simultaneously to the assembly and evaluation of the data for each category. Generally the IHSC found that good correlation of the data suggesting that the proposed categories are appropriate. In one case, the initial assembly and evaluation of the data caused the reorganization of the categories. In this case, originally one category was considered for the C9-C13 Aliphatic Hydrocarbon Solvents. The toxicology endpoint data showed good correlation across this category; however, the products with higher aromatic content (up to 23%) in this category showed somewhat greater respiratory irritation and more water solubility due to the greater solubility of the aromatic fraction, resulting in correspondingly greater potential to cause aquatic toxicity at similar loading rates. To address this difference in irritation, water solubility and aquatic toxicity, it was decided to divide the category into two categories – one with essentially no aromatic content and one with products up to 23% aromatic content. Once the testing is complete, where planned, these additional data will be evaluated to determine whether the categories are valid or need to be reorganized.

Step 6: Prepare category test plan

72. Category test plans have been developed and were submitted to the Sponsor Country (U.S.) for evaluation and consideration prior to submission to OECD.

Step 7: Conduct necessary testing

73. Underway for those categories that have been evaluated by EPA.

Step 8: Evaluate new and existing data for the category and make robust study summaries for new data

74. To be completed upon completion of testing.

Example F: INORGANIC NICKEL COMPOUNDS.

[Note: Inorganic nickel compounds have not been assessed by SIAM yet. The description below is based on the work of the Danish Environmental Protection Agency under the OECD SIDS and the EU existing chemicals programmes, as well as the discussions held at the OECD workshop on the development and use of chemical categories held in January 2004. The descriptions below might have to be revised once the compounds have undergone assessment at SIAM.]

Step 1: Identification of structure-based category and its members:

75. The category is initially defined as "nickel and nickel compounds". This description is a category already widely used in EU legislation. "Nickel and nickel compounds" includes over 300 compounds of very diverse chemical structure. Numerically, organic nickel compounds outnumber inorganic nickel compounds. The category includes a number of complex compounds, many of which are waste products. The wide diversity of chemical types suggests that whilst it is useful as a category in identifying compounds that contain nickel and may therefore potentially be a source of nickel release, it is not a useful category in the sense that it provides a basis for predicting effects that are similar to all members of the group.

76. A second type of grouping of nickel compounds is also used. This divides nickel compounds into five groups: Metallic nickel, oxidic nickel, sulphidic nickel, soluble nickel and nickel carbonyl. These groups reflect the nickel compounds seen during nickel refinery production, rather than the wider range of nickel chemicals on, or potentially on, the market. These different categories have been used in some countries as the basis for different Occupational Limit Values (OELs) based on differences in the types and potency of different mammalian toxicological effects.

77. There are a number of assumptions underlying any grouping of nickel compounds for estimating their biological properties. The main assumption is that it is the nickel ion that is responsible for the effects to be assessed. This is considered to be a reasonable assumption for the majority of the inorganic anions of nickel compounds and for some organic anions. This implies that in the case of inorganic metal salts, the hazard assessment is based on the known toxicity of the cation.

78. The basis of any grouping would therefore be the water solubility of the nickel salt. Two reports prepared for the Danish EPA by Lars Carlsen[1] have collected and assessed the available data for water solubility of inorganic nickel compounds (Carlsen, 2001a) and organic compounds (Carlsen, 2001b).

79. For inorganic nickel compounds, a grouping of inorganically based nickel species has been suggested. Nickel metal and nickel metal compounds can all be considered as insoluble. Nickel oxides and mixed metal oxides are also very similar in terms of their solubility. In the table below, a grouping of the nickel ligands with Group 13, 14, 15, 16 and 17 ligands is suggested. The term 'insoluble' means that the solubility of the species is less than 10^{-4} mol/L, 'slightly soluble' covers the solubility range 10^{-4} - 10^{-2} mol/L, 'soluble' the range 10^{-2} - $5 \cdot 10^{-1}$ mol/L and 'very soluble' refers to solubility above $5 \cdot 10^{-1}$ mol/L.

80. It should be noted that the group of "insoluble" compounds, with solubility < 10^{-4} mol/L, may nevertheless have a solubility in excess of 1 mg/L, depending on the actual solubility and the molecular

[1] Carlsen L (2001a): Aqueous Solubilities and Complex Stabilities of Ni(II) Species. Part I: Inorganic Ligands. Draft report to the Danish EPA.
Carlsen L (2001b): Aqueous Solubilities and Complex Stabilities of Ni(II) Species. Part II: Organic Ligands. Draft report to the Danish EPA.

weight. Hence substances conventionally thought of as "insoluble" by chemists or toxicologists may still be sufficiently soluble to be regarded as such in evaluating effects on the aquatic environment.

Grouping of nickel species based on inorganic ligands in water (from Carlsen, 2001a).

	Group 13	Group 14	Group 15	Group 16	Group 17	Misc.
Insoluble	Ni_XB	Ni_XSi	Ni_XP_Y Ni_XAs Ni_XSb_Y $Ni_2P_2O_7$ $Ni_3(AsO_3)_2$ $Ni_3(AsO_4)_2$ $Ni(AsO_3)_2$	Ni_XS_Y Ni_XSe Ni_XTe		$Ni_2Fe(CN)_6$
Slightly soluble		$Ni(CO)_4$ $Ni(CN)_2$ $NiCO_3$ $Ni(HCO_3)_2$	$Ni_3(PO_4)_2$ $Ni[NiP_2O_7]$	$NiSO_3$[a] $NiSeO_3$	$Ni(IO_3)_2$	$Ni_2Fe(CN)_5NO$
Soluble				$NiK_2(SO_4)_2$	NiF_2	
Very soluble	NiB_6O_{10} $Ni(BF_4)_2$	$Ni(SCN)_2$ $NiSiF_6$	$Ni(NO_3)_2$ $Ni(H_2PO_2)_2$	$NiSO_4$ $Ni(SO_3NH_2)_2$[a] $NiSeO_4$	$NiCl_2$ $Ni(ClO_3)_2$ $Ni(ClO_4)_2$ $NiBr_2$ $Ni(BrO_3)_2$ NiI_2	

81. No comparable grouping of organic ligands has yet been carried out (Carlsen, 2001b). In contrast to the inorganic nickel compounds it is not obvious how to group the organically based species based on solubilities alone. Aqueous solubilities are not unexpectedly seen to decrease with increasing molecular weight and increasing carbon content of the ligand. On the other hand, the introduction of hydrophilic and/or polar functional groups, such as OH, C=O, COO^-, NH, SH and SO_3^- cause increased solubilities. Further it should be emphasized that the solubility of the complexes cannot immediately be related to the solubility of the single ligands. Hence, it seems more appropriate to group organically based nickel complexes based on the stability of the complexes. As a first attempt, grouping the individual complexes based on the nature of the ligand appears as an obvious choice, even though significant variations in stability may prevail within the single groups. However, a number of nickel salts of simple organic acids can be considered to behave in a similar way to inorganic salts with a similar solubility.

Step 2: Gather published and unpublished data for each category member.

82. There is a vast database on the human health effects of nickel compounds. A search in Toxline gave 2538 hits for nickel and toxicity, 5077 hits for nickel and effects and about 16000 hits for nickel and sensitisation. However, the data available for any individual nickel compounds can vary considerably. The two compounds for which there is data that covers most endpoints are the two soluble compounds, nickel chloride and nickel sulphate. Much of the database relating to nickel metal is linked to sensitisation. On the

other hand, there is virtually no data at all for most nickel compounds. In particular, data on the organic nickel compounds is extremely limited.

Step 3: Evaluate data for accuracy.

83. Much of these human health data have been reviewed in good quality reviews including UK HSE (1987)[2], IARC (1990)[3], IPCS (1991, 1996)[4], US ATSDR (1997)[5] and a Nordic Expert Group (Aitio, 1995)[6]. NiPERA in collaboration with Eurométaux have also produced a criteria document for nickel and nickel compounds for the European Commission (NiPERA 1996)[7]. Toxicology Excellence for Risk Assessment (TERA) has prepared a toxicological review of soluble nickel salts for Metal Finishing Association of Southern California Inc., US-EPA and Health Canada (TERA 1999)[8].

84. In depth reviews of metallic nickel, nickel sulphate, nickel chloride, nickel nitrate and nickel (hydroxy)carbonate have been prepared by the Danish EPA.

Step 4: Construct a matrix of data availability.

85. A matrix of available data included in the draft risk assessment reports prepared under the OECD SIDS and the EU existing chemicals programmes is shown below for nickel metal, nickel sulphate, nickel chloride, nickel nitrate and nickel carbonate[9].

86. Data is also available for some other nickel compounds in the reviews quoted above and from the data included in IUCLID. As no substance-specific reviews have been carried out on these substances, the

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[2] Toxicity Review 19. The toxicity of nickel and its organic compounds. Fairhurst & Illing. London. HMSO. ISBN 0 11 883961 6

3 IARC Monographs on the evaluation of carcinogenic risks to humans, Volume 49, Chromium, nickel and welding. IARC, Lyon, France, 1990. pp. 257-446.

4 Environmental Health Criteria 108: Nickel. World Health Organisation, Geneva. 383 p.; IPCS (1996): Guidelines for drinking water quality. Volume 2. Health criteria and other supporting information. World Health Organisation, Geneva, 1996 p. 308-313.

5 Toxicological Profile for Nickel. September 1997. US Department of Health and Human Services, Public Health Service.

6 Nickel and nickel compounds. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. Arbete och Hälsa vetenskaplig skriftserie 1995:26, no 119. Solna: Arbetslivsinstitutet, 1995: pp. 1-61.

7 Occupational exposure limits: Criteria Document for nickel and nickel compounds. Volume I: Summary, Conclusions and Recommendations; Volume II: Assessment of Occupational Exposures; Volume III: Health Assessment of various species of Nickel. Prepared by NiPERA in collaboration with Eurométaux for the European Commission, Directorate General V. Public health and Safety at Work Directorate. Batiment Jean Monnet, Plateau du Kirchberg. L-2920 Luxembourg.

8 Toxicological review of soluble nickel salts. Prepared for: Metal Finishing Association of Southern California, Inc., US Environmental Protection Agency and Health Canada. Prepared by Toxicology Excellence for Risk Assessment (TERA) under subcontract in part with Science Applications International Corporation (SAIC). EPA Contract #68-C7-0011. March 1999.

9 The compound reported as a HPV chemical to IUCLID was nickel carbonate (CAS No. 3333-67-3). In the course of subsequent discussions with the Industry, it became clear that the marketed product was in fact a nickel hydroxycarbonate. For administrative purposes, the commercial product is considered to be the 1:2 hydroxycarbonate, [carbonato(2-)] tetrahydroxytrinickel, (CAS No. 12607-70-4) which is also included in the TSCA Inventory. As it is not always clear from the study reports which precise carbonate has been tested, the results are shown as "nickel carbonate".

data available for each substance is regarded as indicative only. Further work is needed to refine this matrix.

87. In addition data is available on the EU provisional categorization supplied by the producer/importer from IUCLID is available for a number of other nickel compounds, including a number of organic compounds and complex waste products such as slimes and sludges. It is not clear whether these have been based on experimental evidence or on assumptions about the properties of the compounds (i.e. application of a group approach).

88. The main nickel compounds studied are those directly associated with the (refinery) production of metallic nickel, and nickel alloys. Some of the intermediate products (nickel matte, ferro-nickel) in this production process do not appear to have been studied. The data on nickel compounds not directly associated with these processes appears to be very limited. The information on "downstream" nickel compounds, and in particular, the organic nickel compounds, is limited. The information available from IUCLID is difficult to interpret as there is little or no experimental data reported for these substances.

Matrix of data availability on selected nickel compounds.

Nickel compound	Environ-mental fate	Ecological effects*			Human Health effects **			
		Fish acute	Daphnid acute	Daphnid chronic	Acute	Repeated dose	Mutagenicity	Developmental
nickel metal* **	dissolution protocol	-	-	-	√	√	(√)	-
nickel oxide	transforma-tion test	√	√	-	√	√	√	-
nickel sulfide / subsulfide	screening test	-	√	-	√	√	√	-
nickel dihydroxide	screening test	-	√	-	√	-	(√)	-
"nickel carbonate"	dissolution protocol.	-	-	-	√	(-)	(√)	-
nickel acetate	soluble	-	-	√	√	-	√	-
nickel sulphate	soluble	√	√	√	√	√	√	√
nickel chloride	soluble	√	√	√	√	√	√	√
nickel nitrate	soluble	√	√	√	√	-	√	-
nickel carbonyl	soluble	-	√	-	√ ****	-	-	-

Key: "√" denotes data available for the substance/endpoint. There may not necessarily at present be agreement on the interpretation of this data. "(√)" indicates that there is some data, but that additional data may be needed. "(-)" indicates only very limited data from which no conclusions can be drawn. "-" denotes no data available.
Shaded areas show six possible subgroups (the five subgroups shown in step 1 and sparingly soluble nickel hydroxide and carbonate).
*: data concerning other endpoints and species are available and are being considered.
**: data is also available for sensitisation and carcinogenicity
***: nickel metal powder (INCO123) and nickel granules have been tested. Only the powder has been tested in the 28 d dissolution test however
****: data available for inhalational exposure. Data for other nickel compounds is oral data only.

89. The matrix shown above includes the main SIDS endpoints. However, major concerns with nickel and nickel compounds are related to sensitisation and carcinogenicity, endpoints not included in SIDS. Evaluation of these endpoints is important in the evaluation of this particular group of substances.

Step 5: Perform an internal assessment of the category.

90. The subgroup for which most data is available are the soluble nickel salts. The available data suggests that "read-across" within this group is justified. The available data also suggest that the effects of the different nickel compounds are related to water solubility, although different endpoints may behave differently.

91. In applying the aquatic hazard classification rules for nickel compounds, soluble and slightly soluble compounds can be distinguished. For the soluble compounds, no T/D protocol is required. For slightly soluble compounds, the use of T/D protocol, i.e. solubility dependency of pH at environmentally realistic pHs is used.

92. Acute oral toxicity decreases with decreasing water solubility and is of concern for soluble and slightly soluble compounds. Inhalational repeated dose toxicity on the other hand is shown by both soluble and insoluble nickel compounds. There is also evidence of *in vivo* mutagenicity for both soluble and insoluble compounds, although the evidence for insoluble compounds is much less than for soluble compounds. Whilst there is an effect on developmental reproductive toxicity for the soluble nickel compounds, there is little data on which to evaluate this effect in slightly soluble or insoluble compounds.

93. Whilst the environmental effects of nickel carbonyl appear to be consistent with the results expected from its water solubility, its effects on human health are not like any of the other nickel compounds studied. The valence state of nickel in this compound in Ni(0) rather than Ni(II) in most of the other compounds studied.

94. The available data for metallic nickel for key endpoints such as carcinogenicity is not adequate to assess the effects of the metal.

Step 6: Prepare category test plan.
Step 7: Conduct necessary testing.
Step 8: Perform an external assessment of the category.

95. Additional testing is currently underway to evaluate certain aspects of the carcinogenicity of nickel compounds. Metallic nickel is being tested following inhalational administration and nickel sulphate following oral administration.

96. Industry has initiated a research programme concerning the influence of abiotic factors on the (chronic) ecotoxicological effects of nickel using the BLM theory[10].

97. There are no plans at the present time for specific testing aimed at providing data on this category as a whole.

Step 9: Fill data gaps by read-across, extrapolation, interpolation etc.

98. The use of read-across for specific endpoints within the limited group of substances for which data is available is clearly acceptable. This being the case, it seems reasonable to consider to what extent the same approach can be applied to the much larger group of "nickel and nickel compounds".

99. In cases where there are clear similarities to the compounds considered above, the use of read-across to evaluate the hazards of these compounds would seem justified. For example, soluble nickel(II)

[10] Biotic Ligand Model

salts would be expected to show the same effects as the other soluble salts evaluated on the basis of their measured data.