

*MANUAL FOR INVESTIGATION OF HPV CHEMICALS*

**CHAPTER 2: SIDS, THE SIDS PLAN AND THE SIDS DOSSIER<sup>1</sup>**

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<sup>1</sup> This document was prepared by the OECD Secretariat based on the agreements reached in the OECD Existing Chemicals Programme up to May 2002.

## 2.1.Introduction

This chapter describes the Screening Information Data Set (SIDS) (section 2.2) - the minimum amount of data that is required for making an initial hazard assessment of HPV chemicals which has been agreed upon by OECD. The central role of the SIDS Dossier (section 2.4) is described where all relevant study data and information available on an HPV chemical, including that on non-SIDS elements, are collected in a standard manner. A procedure for initial collation of all available data and determining the need for any additional SIDS testing is discussed. The SIDS Plan (section 2.3) lays out the Sponsor's course of action with respect to the use of existing, surrogate or new data.

## 2.2 The Screening Information Data Set (SIDS)<sup>2</sup>

### 2.2.1 Overview

This Section presents the information and data needed to comprise the Screening Information Data Set (SIDS). It also provides guidance for determining adequacy of the existing data and guidance for the collection of additional data. Finally, it describes how to prepare a SIDS Plan and distribute it among Member countries for comment and approval.

### 2.2.2 SIDS Content

The content of the Screening Information Data Set (SIDS) was adopted in November 1989 and revised in February 2000. The SIDS content, organised under five headings: Substance Information, Physical Chemical Properties, Environmental Fate, Environmental Toxicology, and Mammalian Toxicology, is presented below. Comments on the need for specific data are found at appropriate locations in the outline below.

#### Substance Information

- Chemical Identity
  - CAS Number(s)
  - Name (OECD name(s))
  - CAS Descriptor (Only required for inorganic chemicals)
  - Structural Formula
  - Composition of the chemical(s) being assessed (Composition of the assessed substance is strictly speaking not a SIDS element. The information allows for a comparison with the test substance which was used in the different tests. This can influence the reliability of certain studies. It is therefore strongly recommended that information on the composition of the produced and marketed substance is made available. In cases where confidentiality issues are involved, the values can be reported in ranges.):
    - For a single chemical: degree of purity, known impurities or additives, difference of impurities among products, details of stereo-isomers if relevant;
    - For mixtures: percentages or range of percentages of mixture components, known impurities or additives, differences among products;

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<sup>2</sup> The content of the SIDS was agreed at the 13<sup>th</sup> Joint Meeting of the Chemicals Group and Management Committee of the Special Programme on the Control of Chemicals (November 1989). The 30<sup>th</sup> Joint Meeting in February 2000 agreed to revise the SIDS to reflect the refocused HPV Chemicals Programme, primarily moving the consideration of detailed exposure information and the need to conduct terrestrial toxicity testing to the post-SIDS stage.

For Class 2<sup>3</sup> compounds: typical composition and molecular weights, known impurities or additives, differences among products;

For streams<sup>4</sup>: typical descriptors, known impurities or additives, differences among products, basic elements of physical-chemical properties (e.g. water solubility, boiling point range, Log K<sub>ow</sub>, vapour pressure, etc.).

- Quantity (estimated production and/or import volume)
- Use Pattern (categories and types of use)
- Sources of Exposure

A major refocusing of the HPV Chemicals Programme was agreed upon and initiated in 1998. Under the refocused HPV Chemicals Programme, a reduced amount of exposure information is required – and at least that which pertains to the production and use of the chemical in the Sponsor country – in order to put the initial hazard assessment in context. The following guidance is applicable to the above three SIDS elements: quantity, use pattern and sources of exposure. Readily available information on exposure to the chemical should be summarised to provide some understanding of sources of exposure. If such information is not available from non-sponsor countries at least that from the Sponsor country must be included. The human populations for which there is a potential exposure to the chemical should be identified with specific consideration of occupational exposure, consumer exposure and indirect exposure of man via the environment. General information on the environmental release pattern and environmental compartments exposed should be provided. These considerations should be based on readily available general information on exposure, the use pattern and physical-chemical properties of the chemical. It is not necessary to conduct exposure modelling or monitoring for the purposes of SIDS initial assessment but available overview information in this regard may be useful to present.

### Physical-Chemical Properties

- Melting Point
- Boiling Point
- Relative Density (required for inorganic chemicals, and should be provided if readily available for organic chemicals)
- Vapour Pressure
- Partition Co-efficient: n-Octanol/Water
- Water Solubility
- Dissociation Constant (for substances normally capable of dissociation)
- Oxidation-reduction Potential (required for inorganic chemicals; may be required for certain organic chemicals)

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<sup>3</sup> Class 2 denotes a chemical that occurs as a complex mixture of different individual substances rather than existing as a single chemical species with a well-defined molecular structure (e.g., a paraffin wax). Class 2 compounds also include unknown or variable composition complex reaction products, biological materials (UVCB). UVCB substances can for example be described by structural features (e.g. acid chlorides, alkaline earth compounds, polyoxyalkylenes), a significant precursor (e.g. Castor Oil or Tallow) or by a more general description (e.g. Resins or Waxes.)

<sup>4</sup> A stream is defined as a material that is created in a chemical process and exists as a process stream that is a complex mixture of individual substances. The stream may be isolated and treated as a product without separating out its many individual components as pure chemicals. The stream may be defined by the process conditions that created it.

## Environmental Fate

- Photodegradation
- Stability in Water (not required for classes of chemicals whose molecular structure does not possess functional groups subject to hydrolysis, or are generally recognised to be resistant to hydrolysis. In these cases a qualitative statement can be provided.)
- Transport and Distribution between Environmental Compartments including Distribution Pathways [including Henry's Law constant, aerosolisation, volatilisation, soil adsorption and desorption, either based on experimental data or if not available or appropriate, calculated using structure-activity relationships (SARs)]
- Aerobic biodegradability

## Environmental Toxicology

- Acute Toxicity to Fish
- Acute Toxicity to Daphnia
- Toxicity to Algae
- Chronic Toxicity. Necessity determined based on physical chemical properties of the chemical. Any new data required should be collected using the most sensitive species (fish, daphnia or algae) within limitations of the chemical properties (see section 2.3.2 for further guidance on test selection).
- Terrestrial Toxicity. The need for testing will normally be addressed at the post-SIDS stage. However, if significant exposure is expected or identified in the terrestrial environment (soil), appropriate terrestrial toxicity tests should be considered at the SIDS level (see section 2.3.2 for further guidance on test selection). Taking into account animal welfare considerations, the need for avian toxicity testing should only be considered at the post-SIDS stage.

## Mammalian Toxicology<sup>5</sup>

- Acute Toxicity (either by oral route, dermal route or inhalation; required only on the most relevant route of exposure)
- Repeated Dose Toxicity. The protocol for new studies should specify the use of the most relevant route of exposure.
- Genetic Toxicity. Two end points required, generally point mutation and chromosomal aberrations.
- Reproductive Toxicity. Requires data to assess fertility and developmental toxicity.
- Experience with Human Exposure (if available).

### **2.2.3 Existing SIDS Data**

There is a need to identify, assemble and review data relevant to the SIDS elements. A three- stage data gathering approach has been found effective for locating all relevant data for review.

#### Stage 1

Firstly, industry should search their files for privately held data on the chemical. All available information should be noted since refinement of the data search will take place at stage 3.

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<sup>5</sup> Skin irritation, eye irritation and sensitization are not SIDS elements. Available data on these endpoints should always be reported.

## Stage 2

Stage 2 involves a broad search of databases and the published literature to obtain all available data on the chemical. As far as possible, original publications should be retrieved. The data sources listed below are not an exhaustive list but provide a useful starting point.

- Search of published scientific literature through the use of e.g. CHEMLINE, TOXLINE, TOXBACK, TOXLIT. Health effects data are available online through the National Library of Medicine network. Other broad-based databases which may be of use include the following: STN easy on line, Poltox CD-ROMs 1966-2000, ECOTOX, Medline, Enviroline, Embase, Aqualine, ASFA 3, Aquatic Pollution and Environmental Quality, Chemical Abstracts, SciSearch, Environmental Chemical Data Information Network (ECDIN), BIOSIS, Pesticide Fact File, Chemtox TOXLINE, OSHROM, HSELINE.
- In the event that original study reports may not be obtained, standard references which are known to publish “peer reviewed” data should be searched. Examples of useful references are as follows:
  - *Merck Index* – For physical-chemical properties and use information. Available as a book and online in the STN network.
  - *Condensed Chemical Dictionary* – For physical-chemical properties and chemical use information. Book.
  - *Kirk-Othmer Encyclopedia* – For chemical use information. Book.
  - *Patty's Industrial Hygiene and Toxicology* – For health hazard data. Book.
  - *USEPA IRIS* – For toxicity data, NOAELs, RfDs, RfCs and cancer slope factors. Available online and as diskette.
  - *ATSDR Toxicological Profiles* – For health effects, use and exposure data. Published reports and CD-ROM.
  - *NTP (National Toxicology Program)* – For health effects, use and exposure data. Published reports and on-line (by subscription.)
  - *IARC (International Agency for Research on Cancer)* – For health effects, use and exposure data. Published reports and CD.
  - *OSHA (Occupational Safety and Health Administration)* – For workplace exposure standards and their basis. Federal Register, other publications and online at <http://www.osha.gov/>.
  - *ACGIH (American Conference of Governmental Industrial Hygienists)* Recommended workplace standards and their basis. Publications and CD-ROM.
  - *AIHA (American Industrial Hygiene Association)* Recommended workplace standards and their basis. Publications and available on-line. Subscription service.

- Physical-chemical properties can also be obtained from standard reference works such as Lide, Hawleys, Condensed Chemical Dictionary; Beilstein; Sax, CRC Handbook of Chemistry and Physics; Bretherick's 'Handbook of Chemical Reactive Hazards'; Handbook of Chemistry, Norbert A. Lange, McGraw Hill; Fire Protection Guide on Hazardous Materials, National Fire Protection Association, Boston; Dust Explosions in the Process Industry, R.K. Eckhoff, Butterworth Heinemann.
- Internationalised reviews such as Concise International Chemical Assessment Documents (CICADs) and Environmental Health Criteria Monographs should be consulted where available. The Environmental Health Criteria (EHC) contain data on use, exposure, human toxicology and environmental toxicology. The more recent EHCs also include a proposal for maximum permissible risk levels (searches may be conducted at <http://www.inchem.org/pages/search.html>)
- Sponsors should search multiple databases to ensure that all existing data have been obtained. Some of the data may not have been "peer reviewed"; however, the information may provide supporting data for a SIDS element. These may consist of some of the following resources:
  - IUCLID – (International Uniform Chemical Information Database) For chemical use, exposure, environmental fate, ecotoxicity and mammalian toxicity. Available on CD-ROM.
  - AQUIRE – (Aquatic Information Retrieval) For aquatic toxicity data. Available online in the CIS network. [TOXNET by the National Library of Medicine (NLM) offers links to Toxline, TRI, HSDB, RTECS and others at [www.toxnet.nlm.nih.gov](http://www.toxnet.nlm.nih.gov). Further, EPA's ECOTOX database covers Aquire, phytotox, terretox at [www.epa.gov/exotox/](http://www.epa.gov/exotox/)].
  - RTECS – (Registry of Toxic Effects of Chemical Substances) For health effects data (Note: mainly positive findings are reported here, other results might be available in other databases). Available online in the TOXNET and STN networks.
  - TSCATS – For unpublished chemical hazard data submitted under TSCA Section 4, 8(d), 8(e) and FYI. Available online in the CIS network or in the NLM network as a subset of TOXLINE.
  - TRI – (Toxics Release Inventory) For environmental release data in the US. Available online and web (<http://www.epa.gov/tri/>).
  - HSDB – (Hazardous Substance Data Bank) For chemical use, fate and health effects data. Online in the TOXNET network.
  - Verschueren, K. Handbook on Environmental Data on Organic Chemicals. Book
  - Lyman, et al, (ed.)(1983) Handbook of Chemical Property Estimation Methods, McGraw-Hill, NY

- Furia (ed.) CRC Handbook of Food Additives, Chemical Rubber Co.
- Fenaroli's Handbook of Flavor Ingredients, Chemical Rubber Co.
- Flick, Industrial Solvents Handbook.
- There may be other national reviews available, for example from the UK Health and Safety Executive (HSE), German MAK commission (DFG Herausgeber, List of MAK and BAT values, Wiley, VCH), German Advisory Committee on Existing Chemicals (BUA reports, S. Hirzel Wissenschaftliche Verlagsgesellschaft), Nordic Expert Group, the Netherlands DECOS. HSE publishes comprehensive reviews for Occupational Exposure standard setting, toxicity reviews and other more focussed documents such as their compendium of asthmagens. These are searchable on hseline, details of which are available at <http://www.hse.gov.uk>.

Appropriate search strategies should be adopted and search terms should be stated in the SIDS Dossier.

### Stage 3

The third stage in the process involves selection of the most appropriate data collected during stages 1 and 2. Peer-reviewed data sources such as those listed above may prove useful in deciding which data is valid and the most relevant.

Information from the data search should be organised and formatted in a SIDS Dossier as described in detail in Section 2.4. Furthermore, the *Guidance for Determining the Quality of Data for the SIDS Dossiers: Reliability, Relevance and Adequacy* (Chapter 3, section 3.1) should be used for determining whether information is satisfactory for use in the initial assessment of a chemical. Since it is not feasible to give guidance to cover every situation it is essential that suitably qualified personnel evaluate all data. The results of the evaluation will influence the decision on further testing.

## 2.3 The SIDS Plan

Once the existing data have been collected and reviewed, it is necessary to decide upon the need for additional adequate data. The Sponsor decides, for each endpoint, as to: the adequacy of existing data (through data, surrogate data, or SAR), or the need to gather additional information through the performance of additional tests. All existing information should be gathered and described in an initial version of the chemical's SIDS Dossier (Section 2.4). (For some chemicals where data exist for all required SIDS elements and the situation is clear-cut, an initial dossier may not be needed, and the sponsors may proceed directly to a full dossier).

### 2.3.1 Determining the Need for Additional Data<sup>6</sup>

To avoid unnecessary duplication of work and possible needless use of animals for testing, it is important that all existing available relevant data be located and reviewed. The requirement to complete any

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<sup>6</sup> The general content of this section is based on a document discussed at the 20th Joint Meeting of the Chemicals Group and Management Committee of the Special Programme on the Control of Chemicals (May 1993).

individual data element of the SIDS by further testing will depend upon the reliability and quantity of data available. In analysing the adequacy of existing data, Sponsors shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Sponsors shall maximise the use of existing and scientifically adequate data to minimise further testing.

When existing data are determined to be inadequate to support the requirements for a SIDS element it should not be automatically assumed that additional tests are required. There are a variety of circumstances in which a SIDS element could be waived or met through other approaches. These include:

*Animal Welfare Considerations.* The statement on animal welfare adopted by the Second High Level Meeting of the Chemicals Group should be taken into account when determining the need for new SIDS testing. To facilitate its consideration it is reproduced here.

*“The welfare of laboratory animals is important. It will continue to be an important factor influencing the work in the OECD Chemicals Programme. The progress in OECD on the harmonization of chemicals control, in particular the agreement on Mutual Acceptance of Data, by reducing duplicative testing, will do much to reduce the number of animals used in testing. Such testing cannot be eliminated at present, but every effort should be made to discover, develop and validate alternative testing systems.*

*“The High Level Meeting invites the Chemicals Group, the Management Committee, the Updating Panel, Lead countries and the Secretariat, to ensure that the spirit of this Declaration is an integral part of their work.” [ENV/CHEM/HLM/M/82.1, para. 95]*

*The Use of (Q)SAR.* Appropriate information derived from (Quantitative) Structure Activity Relationships can be of assistance in determining the need for new testing. The *Guidance on the Use of Structure-Activity Relationships (SAR) in the HPV Chemicals Programme* (Chapter 3, section 3.3) should be consulted.

*The Use of Chemical Categories.* 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. See also section 2.3.5 and the *Guidance on the Development and Use of Chemical Categories in the HPV Chemicals Programme* in Chapter 3 (section 3.2).

*Practical Considerations.* Practical reasons for completing less than the SIDS for an individual chemical include the availability of information concerning isomers that have a similar structure-activity profile; closely related homologues; relevant precursors and breakdown products along with information on metabolism and degradation (see section 2.3.4 on analogues). As a general approach, for each particular endpoint, the use of range-finding tests may be an appropriate first step to establish relative levels of toxicity between isomers. Less than a standard SIDS testing regime may also be appropriate for chemicals that are unstable under test conditions or for reasons based on their physical/chemical properties. For example:

- It might not be appropriate to test the aquatic toxicity of gases, and QSAR estimations might be sufficient to fill the corresponding SIDS elements.
- Testing to obtain dissociation constant data is not needed for chemicals or classes of chemicals generally known not to dissociate (e.g., hydrocarbons).

- Testing for stability in water is not needed for substances generally recognised to have molecular structures or possess only functional groups (e.g., hydrocarbons) that are generally known to be resistant to hydrolysis.
- For substances which have an obviously high boiling point and low vapour pressure (e.g. some inorganic or organic salts), an estimation of these two endpoints could be sufficient.

For some chemicals standard tests may be irrelevant or not provide meaningful results. Testing should not be conducted, when it cannot be done safely. When testing is not practical or meaningful for reasons such as stated above, the reason for not testing should be given in the SIDS Dossier and/or the SIDS Initial Assessment Report (SIAR, see chapter 5).

*Limited Exposure Potential, (especially for intermediates which have a limited exposure potential).* Reduced testing may be appropriate for a SIDS chemical due to limited exposure potential, depending on production or use scenarios. The considerations below are specific to chemical intermediates. A chemical that is intended to undergo a further deliberate reaction to produce another industrial substance is considered an intermediate. In the context of the HPV Chemicals Programme, reduced testing may be permissible for intermediates handled in a specific manner that results in a limited potential for exposure. Eligibility for reduced testing is available only for chemicals whose entire production is used as an intermediate. Specific circumstances and the associated reduced data requirements are given below:

- a) Non-isolated intermediates, i.e. those chemicals whose life cycle is restricted to the reaction vessel and its specific equipment. All forms of repeat dose testing may be waived. If the releases to the aquatic environment can be shown to be negligible, testing on acute toxicity towards fish might be waived if this endpoint can be adequately filled with (Q)SAR estimations.
- b) Isolated intermediates that are stored in controlled on-site facilities. If repeat dose data are available, reproductive and developmental toxicity may be waived. If repeat dose data are not available, testing using OECD Test Guideline 422 should be considered on a case-by-case basis.
- c) Isolated intermediates with controlled transport, i.e. to a limited number of locations within the same company or second parties that use the chemical in a controlled way as an intermediate with a well-known technology. If repeat dose data are available, reproductive and developmental toxicity may be waived. If repeat dose data are not available, testing using OECD Test Guideline 422 should be considered on a case-by-case basis.

Data that support claims for exemptions from SIDS testing based on limited exposure must meet criteria for reliability and adequacy of SIDS data. This requirement for reliability and adequacy of data also applies to substantiated evidence of existing or potential exposure made by a Member country that objects to the reduced data requirement based on limited exposure.

Specific information is required to support a claim for reduced testing. The details are set out below:

#### 1. Information on sites

- Number of sites
- Basis for "closed process" conclusion at each site:
  - process described in enough detail to clarify the basis for claiming that the process is closed;
  - monitoring data, including the limits of detection;
  - if monitoring data are not available, statement that no monitoring has taken place and basis for believing, in the absence of data, that the chemical has not been released and that exposure does not occur.

- Data on "presence in distributed product" or, in the absence of data, the basis for believing it is not present (The basis can be an explanation from the manufacturer why it is unlikely that the chemical is not or no longer present in a distributed product.). Information on conversion rate and presence after purification should be available.

2. Information on transport. If transport occurs, then in addition to the above, provide the following:

- Mode of transport (e.g. water, truck, rail, pipeline);
- Volume (annual);
- Types of consignments (e.g. bulk or drums);
- Controls during transport and transfer at dispatching and receiving sites (placards, labels, etc.).

3. Supporting evidence from a data search showing that the chemical is not present in other end-products. (The basis can be an explanation from the manufacturer why it is unlikely that the chemical is present or used in a distributed product.).

For chemicals other than intermediates, the possibility of reduced SIDS testing exists based on considerations of limited potential for exposure. Adequate experience is not yet available though to develop suitable criteria to define such considerations in sufficient detail.

A proposal for reduced testing due to a limited exposure potential (including for intermediates) must be put forth to other Member countries to provide an opportunity for their review and comment, preferably through the use of the Electronic Discussion Group for Existing Substances not Assigned to a SIAM (pre-SIAM EDG). A Member country can object to the reduced SIDS testing requirements if they provide substantiated evidence of existing or potential exposure in their country. In cases where no agreement can be reached via the EDG the SIAM will decide.

The justification for reduced testing should be reflected in the dossier entry for the endpoint that was not completed, so that when data searches are performed at a later stage, the reason for not performing the test can be retrieved.

### 2.3.2 Notes on Test Selection

Any new SIDS testing that is required must be performed according to internationally acceptable Test Guidelines and Good Laboratory Practices.<sup>7</sup> Test reports should contain suitable, signed GLP and quality assurance statements.

In cases where the SIDS Plan proposes complex or unorthodox approaches, the Sponsor is encouraged to post the SIDS Plan on the pre-SIAM EDG early in the process for review and comment by other SIDS Contact Points.

For aquatic effects testing, prolonged/chronic toxicity testing should be considered in addition to acute tests if there is concern for long-term effects. If there is concern for possible long-term effects, for example based on the structure and properties of the chemical such as a high Log K<sub>ow</sub> and a lack of readily biodegradability, and there is potential for significant exposure to the aquatic environment, prolonged/chronic toxicity testing may be considered. Any new data should be collected using the species that had the lowest L/EC<sub>50</sub> in the acute tests, taking into account animal welfare considerations and any practical limitations due to the chemical properties. If algae are the most sensitive species, a growth

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<sup>7</sup> OECD Test Guidelines and GLP or equivalent Test guidelines and GLP principles of Member countries.

inhibition test with a different algal species or with a different aquatic plant such as *Lemna* should be considered.

The need for testing will normally be addressed at the post-SIDS stage. However, if significant exposure is expected or identified in the terrestrial environment (soil), appropriate terrestrial toxicity tests should be considered at the SIDS level. Factors to consider when determining whether terrestrial toxicity testing should be a SIDS requirement include:

- Potential for reaching the terrestrial environment based on use and transport patterns and disposal practices, e.g., take into account all phases of the chemical's life cycle;
- Physical-chemical properties indicate that the compound may be persistent, has a potential to bioaccumulate, or that a major portion may partition to the soil; and/or
- Monitoring data indicate residues in soil, sewage sludge or groundwater.

The terrestrial test selected at the SIDS stage should be appropriate to the receiving environmental compartment (e.g. in the case of sewage sludge, toxicity to earthworms and plants). In addition, attention should be given to the potential for cross-media distribution. Initially, a test should be performed on terrestrial invertebrates and/or plants. The artificial soil test is preferred because the paper contact test is not truly representative of the natural habitat. Taking into account animal welfare considerations, the need for avian toxicity testing should only be considered at the post-SIDS stage.

For mammalian toxicity, with a few exceptions all substances should be tested by the oral route. Dependent upon the most important route of human exposure and physical-chemical properties of the substance, the dermal or the inhalation route could also be considered. Gases and vapours should be tested only by the inhalation route. A different route of exposure may be used if it is generally regarded as an appropriate route for a particular protocol.

For oral acute toxicity to mammals, guidance regarding the choice of the most appropriate Test Guideline to enable particular data requirements to be met while reducing the number of animals used and animal suffering can be found in the OECD Guidance Document on Acute Oral Toxicity Testing (OECD Series on Testing and Assessment Number 24, <http://webnet1.oecd.org/oecd/pages/home/displaygeneral/0,3380,EN-document-524-14-no-21-5745-0,FF.html>). The Guidance Document also contains additional information on the conduct and interpretation of OECD Test Guidelines 420, 423 and 425. Consideration should be given to the possibility of using data from analogues or repeated dose toxicity studies on the same substance as a substitute.

Regarding genetic toxicity, guidance on testing can be found in annex 1 of this chapter (section 5.6 and 5.7 of annex 1) as well as in section 4.3 "Provisional guidance for the initial assessment of health effects". Results on two different endpoints should be available, generally gene mutation and chromosomal aberration. If a test result on genetic toxicity *in vitro* is positive, it is necessary to perform a test on genetic toxicity *in vivo* such as the micronucleus test or metaphase analysis of bone marrow cells. For chemicals which are *in vitro* mutagens and are handled and used as if they were *in vivo* mutagens, then any further *in vivo* tests may be considered for post SIDS assessment.

For health effects testing the reproduction toxicity requirements may be satisfied through the use of data from several studies. Three typical examples are provided below:

- Requirements are met when a developmental toxicity study is available together with a 90-day repeated dose study that sufficiently documents that male reproductive organs were examined histologically and indicate no effects. If results from a developmental toxicity study are not available then such a study is required (e.g. OECD Test Guideline 414).

- When either a 90-day (with no evaluation of male reproductive organs) or a 28-day repeated dose study is the only repeated dose study available, it is recommended that at least a reproduction/developmental toxicity screening test (e.g. OECD Test Guideline 421) be carried out, in order to satisfy the requirements for the reproductive/ developmental toxicity endpoint.
- When a repeated dose toxicity test of 28-days or longer is not available, then a combined repeated dose toxicity test with a reproductive/developmental screening test (e.g. OECD Test Guideline 422) can be carried out to satisfy the requirements for repeated dose and reproductive/developmental toxicity. (This option uses the lowest number of test animals to satisfy both the repeated dose and the reproduction toxicity requirements.)

### 2.3.3 Determining What Chemical to Test

In general, tests should be carried out with the substance as manufactured and to which humans or the environment is exposed. However, several practical issues should be considered in the selection of the actual test substance. Several are summarised below:

- To avoid interference from additives and impurities, when practical, it is recommended that tests for physical-chemical properties be conducted on the purest form available, which allows the substance to remain stable, because they give basic information on a specific chemical.
- SIDS tests should generally be carried out on the typical commercial substance with any essential additives (e.g. stabilisers) and impurities it normally contains in order to know the effects of the marketed product. Ideally, the same batch of substance should be used for all tests. If the marketed product contains large proportions of water, mineral oil or other solvents, consideration should be given to their removal from the test substance so that the SIDS chemical may be evaluated at concentrations that have biological relevance.
- Highly reactive chemicals may not be stable enough for experiments to be conducted; hence testing may not be practical. In these cases, it may be useful to selectively examine breakdown products for possible adverse effects; and, where a compound is of limited stability, it may be desirable to design individual ways for testing the potential effect for particular endpoints. For testing aquatic toxicity with reactive substances, see also the *Guidance document on aquatic toxicity testing of difficult substances and mixtures* (OECD Monograph No 23, Series on Testing and Assessment).

### 2.3.4 Data from analogues

It is appropriate to investigate the use of analogues or surrogates to assist in providing supplemental data to reduce possible testing needs. In some situations data from another chemical can be used, such as:

- isomers which have similar structure activity profiles;
- closely related homologues;
- relevant precursors and breakdown products, along with information on metabolism and degradation.

The data of the related compound should be inserted in the SIDS dossier for the chemical, clearly stating the identity (chemical name and CAS No.) of the related compound (test substance). When data for

an analogue chemical are used to fill one or more endpoints, the data for the analogue's other endpoints must be compared and discussed in relation to the main chemical to shed light on the similarities and differences in the properties of the main chemical and its analogue.

### 2.3.5 Chemical Categories

A chemical category 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 methylene group difference between adjacent members of the alpha-olefins). 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 (e.g. linear alkylbenzene mixtures).

If the available 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.

A clear explanation needs to be provided as to why a category is being proposed and how the presented data are going to be used in relation to the category and the testing plan. It is recommended that a SIDS Dossier be prepared for each individual chemical within the category. In section 1.03 of the SIDS Dossiers of each chemical forming the category (see annex 1), the identity of the substances forming the category should be listed together with the rationale behind the formation of the category. At a minimum, data on each chemical's physical chemical properties should be provided, as it will vary per chemical. For the preparation of the SIDS Dossiers for each individual chemical within the category, sponsors may choose between two options:

1. Each SIDS Dossier would only contain the information and Robust Study Summaries which are available for each specific substance forming the category. In situations where data from another chemical within the category is used to complete an endpoint, a reference to the SIDS Dossier(s) containing the data would be inserted in each of the dossiers in which the endpoint is not filled with data. If information from another related chemical outside of the category is used to complete an endpoint, the study results of the related compound should be inserted in the SIDS dossier for the chemical, clearly stating the identity (chemical name and CAS No.) of the related compound (test substance).
2. Each SIDS Dossier would contain full data sets for all the SIDS required endpoints (even if another test substance was used to complete this endpoint). If information from another chemical within the category (or from another related chemical outside of the category) is used to complete

an endpoint, then it would be included in that single dossier. The study result from the related chemical should be inserted into the dossier for the chemical it is representing, clearly stating the identity (chemical name and CAS No) of the related compound (test substance).

As more experience is gained with the assessment of categories, the above guidance can be revised if necessary.

The use of a Data Matrix can help to illustrate the extent to which analogue data is used to fill data gaps. A template of a Data Matrix is located in Annex 1. Further guidance can be found in the *Guidance for the Development and Use of Chemical Categories in the HPV Chemicals Programme* (see Chapter 3, section 3.2).

*Inconsistencies with categories:* The basis for category proposals varies depending on the specific reasons for forming a category. Experience to date has shown that a chemical category proposal may be acceptable for one area of concern for the SIDS elements but not others. As an example, a chemical may be manufactured and produced similarly, have similar physical-chemical properties and environmental fate, but may be expected to react differently in the aquatic environment or behave differently concerning health toxicity. In these cases, it is recommended that the Sponsor thoroughly evaluate the chemicals proposed in the category to determine if possible sub-categories may be required for specific endpoints.

### **2.3.6 Review of the SIDS Plan**

Once the available data are collected in the initial SIDS Dossier they are evaluated and a determination made on the need for additional testing. These decisions, and the logic used in their formulation are assembled in a SIDS Plan. Wherever the sponsor has ascertained that adequate data for a SIDS element are not available and testing is considered unnecessary (e.g. due to limited exposure, use of data from analogues, a category approach), it shall forward a statement to pre-SIAM EDG, together with full justification and relevant supporting data. The statement should provide detailed argument explaining why testing is not needed. Arguments for not testing must be well developed and convincing. When this SIDS Plan is submitted it should be supported by an initial version of the chemical's SIDS Dossier with Robust Study Summaries (described in section 2.4 and Annex 1) that shows SIDS data needs and whether testing is required.

Once the testing plan has been agreed on the pre-SIAM EDG, any additional testing is to be conducted and results incorporated in the SIDS Dossier.

## **2.4 The SIDS Dossier**

### **2.4.1 Overview**

The SIDS Dossier is the basic reference document that contains or cites all readily available data/information on the HPV chemical under investigation. As a basic reference it initially underpins the SIDS Plan and ultimately, with revision, the SIDS Initial Assessment Report (SIAR) (see Chapter 5). To facilitate review of data in the HPV Chemicals Programme it is important that SIDS Dossiers be prepared using a harmonised format. Such format guidance is provided in Annex 1. In addition, Annex 2 provides guidance for entering data into SIDS Dossiers using the IUCLID software (see also section 2.4.2 below).

The SIDS Dossier frequently develops in two stages: initial collection and formatting of data; and an updating or revision stage. In the updating stage the SIDS Dossier is revised through the inclusion of data from new SIDS testing, SAR analyses etc. Robust Study Summaries are developed and included into the

SIDS Dossier for selected key studies as discussed in section 2.4.3. Templates for Robust Study Summaries are found in Annex 1.

#### 2.4.2 Data Collection and Preferred Software

The SIDS Dossier provides information about each SIDS element together with non-SIDS elements (where such information is available and relevant to the assessment) in a standardised format. As detailed in Section 2.2.2, SIDS information is organised under five headings: Substance information; Physical-chemical properties; Environmental fate; Environmental toxicity; and Mammalian toxicity.

The IUCLID software<sup>8</sup> is the preferred format for entering data, and developing a SIDS Dossier, using the standard templates. The dossier can be submitted as an exported electronic IUCLID file, as a hard copy printed directly from IUCLID, or as a copy that has been converted to the Word format. By using the IUCLID software for data collection, efficiencies are gained at the data submission stage. In addition, once an assessment has been finalised in OECD, the data in the SIDS Dossier can be transferred directly from IUCLID to UNEP Chemicals for publication. Step by step procedures for preparing a SIDS Dossier using the IUCLID software are given in Annex 2<sup>9</sup> to this chapter.

Information presented in a SIDS Dossier should be sufficiently reported and referenced with respect to the substance tested, methods used, endpoints examined and results obtained so as to allow reviewers to make an informed judgement of the suitability of the data for its intended use.

All studies containing data relevant to a SIDS element should be cited in the SIDS Dossier. When more than one study exists for a data element, a brief description of the reliability and adequacy of the studies should be presented. Consistency of the study data results should also be summarised.

The reliability of data in the SIDS Dossiers should be determined by the Sponsor using the criteria set out in the *Guidance for Determining the Quality of Data for the SIDS Dossiers: Reliability, Relevance and Adequacy* (see Chapter 3, section 3.1). The following general principles should be used in reviewing and documenting the quality of the data in the SIDS Dossier:

- Each SIDS Contact Point in a Sponsor country must have the opportunity to evaluate the reliability, relevance and adequacy of key and supporting data for a chemical(s). In principle, all OECD Member countries will rely upon their evaluation of the quality, if it is sufficiently documented. The templates for Robust Study Summaries discussed below include a section which describes the rationale for the reliability of the study as well as the process by which the “reliability” decision was taken.
- In general the support data and reports will not be kept confidential [see also OECD Council Act C(83)98(Final) and its OECD List of Non-Confidential Data on Chemicals]. In exceptional cases where data are confidential the data will be made available for review under the conditions set out in the OECD Council Act concerning Exchange of Confidential Data on Chemicals [C(83)97(Final)]. This Council Act applies to specific experts in each country who receive the data.

When a study fails to meet core data adequacy criteria, minimum information should still be provided, e.g. comments explaining why the study is considered inadequate. It is important to record the

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<sup>8</sup> IUCLID - International Uniform Chemical Information Database

<sup>9</sup> It should be noted that this IUCLID Guidance Document, version 1.1 (dated 14 December 2000), refers to IUCLID version 3.1.1, although it has been integrated in the help function of the new IUCLID version 4. An upgrade of the guidance document to the current IUCLID version is planned.

existence of studies - even if regarded as inadequate - because in some cases when seen in a specific context, they may be used to provide sufficient information on a SIDS element, avoiding the need for additional testing. This is particularly true where there may be good data from chemical analogues, which give support for the study result, even though judged inadequate at the initial collection of information.

## 2.4.3 Robust Study Summaries

### 2.4.3.1 General Discussion

A Robust Study Summary should reflect the objectives, methods, results and conclusions of a full study report. Information within a Robust Study Summary must be provided in sufficient detail to allow a technically qualified person to make an independent assessment as its reliability and completeness - minimising the need to go back to the full study report. Given the central role of Robust Study Summaries in providing the basis for the assessment and disposition of a chemical in the HPV Chemicals Programme, the procedure used to review the original study to verify the accuracy of the Robust Study Summary should be described.

In SIDS Dossiers, Robust Study Summaries are of particular relevance for the adequate presentation of any study that is relevant for hazard assessment. This is in general true for “key studies” which are the basis for the data analysis presented in the SIAR (see section 2.4.3.3).

In principle, at least one key study should be summarised in the form of a complete Robust Study Summary for each SIDS element. Under special data conditions, it may be necessary to prepare also Robust Study Summaries for inadequate or invalid studies as further outlined in section 2.4.3.3. Where data on certain elements for the sponsored chemical are not available and surrogate information is to be used, the SIDS Dossier should contain Robust Study Summaries of data on the related compounds (see section 2.3.4) and the identity of the related compounds should be clearly stated under the test substance heading.

### 2.4.3.2 Robust Summary Templates

A series of templates for Robust Study Summaries have been developed for most of the SIDS elements. They have been structured to allow for computerised data entry via IUCLID by describing the items in each Robust Study Summary as “data fields” with allowance for free text. The Robust Study Summary templates have eight sections: Test Substance, Method, Test Conditions, Results, Conclusions, Reliability, References, and Remarks. Templates provide a convenient data management tool by providing prompts for the type of information to include. This will increase the quality of the SIDS Dossier, and description of the study overall.

The Robust Study Summary allows for remarks on the adequacy and relevance of a study and encourages the description of test methodology and detailed results to be included in the SIDS Dossier rather than the SIDS Initial Assessment Report.

The following descriptions of information to be provided in the SIDS Dossier refer to reporting all elements, whether they are SIDS or non-SIDS and whether there is a Robust Study Summary template available or not.

**Test Substance:** This refers to the identity of the chemical. Where possible the purity, percentages of known impurities, and details of any vehicle used should be given. If the chemical used in the specific test was different from the commercial product (purity, additives, different solvent carrier, etc), then those

differences need to be noted. This notation is inserted in the Test Substance Remarks field together with the chemical name, CAS number, purity of the materials, percentages of known impurities, additives, and chemical structure, as appropriate. If the chemical(s) are listed in EINECS, it would also be useful to have its identification number.

**Method:** This section refers to the methodologies used to conduct the study. If the study was done according to OECD Test Guidelines or other widely recognised standard test methods/guidelines (e.g. OECD, ISO, DIN, APHA, and EPA), this should be identified. The year of publication of the guideline should be reported as well. In these instances a full description of the method is not needed; only the name of the guideline, e.g. OECD 421, 'Reproduction/Developmental Toxicity Screening Test' needs to be reported. The same considerations apply for studies run under standard guidelines that have since been superseded. When a non-standard method has been used, details of the method, equivalent to those in an OECD Test Guideline, should be provided. If such information is not available this fact should be noted.

When the test method allows the use of alternatives for certain test parameters (e.g. species); the alternatives chosen should be indicated. In the case of aquatic toxicity tests, it is important to indicate whether nominal or measured concentrations were used.

If there have been deviations from the Test Guideline, then those deviations that will significantly impact either the study reliability or the interpretation of the data need to be individually listed. There may also be situations in which a single study addresses several elements, such as with a study that follows the OECD combined repeat dose/reproduction/developmental (OECD Test Guideline 421). If a key study is available addressing more than one SIDS element, then several Robust Study Summaries would be prepared. Thus the Results and Conclusions sections would be different depending on the endpoint but the Method and Reference section would be the same in each case.

**Test Conditions:** Any relevant information on test conditions on a broader sense, i.e. test system including test conditions, testing procedure e.g. temperature, pH, test system etc, can be listed under this heading.

**Results:** This section includes standard items to be filled in under discrete bullets for additional items that may be needed to adequately assess data for reliability and use. At a minimum, qualitative descriptions of elements where dose-related observations were seen should be described and a NOAEL and LOAEL stated (where relevant) for critical effects together with the rationale for selection of these values (e.g. biological significance, lack of genotoxicity, etc.). In addition, should a study include effects that were not considered to be biological or statistically significant, an explanation should be given.

Expressing results by phrases such as "insoluble in water" is discouraged. A limit test should be performed under such circumstances so that a positive expression, such as "< 0.1 mg/l (analytical limit)", can be entered. Calculated values must be identified and the calculation method should be cited.

**Conclusions:** The conclusions of the author of the study can be noted, together with any comments of the person preparing the Robust Study Summary. The conclusions of the submitter or reviewer of the data should be clearly separated from the conclusions of the author, by indicating the origin of the comments.

**Reliability:** This section can be used to denote the adequacy of data, at the discretion of the person preparing the summary. Data reliability codes can be used, as described in Chapter 3 (section 3.1; *Guidance for Determining the Quality of Data for the SIDS Dossier*). The rationale for the reliability code should be described clearly as should the process by which the "Reliability" decision was made. A rationale supporting selection of the "key study" (see section 2.4.3.3) should be given (where applicable and how the

Robust Study Summary was confirmed as an accurate reflection of the original study data should be described in this section.

**References:** This free text field is to be used by the person preparing the SIDS Dossier to cite full references for the critical studies on which the summary is based. The source of information used to respond (address or fill) to the endpoint should be identified. In general, information should be taken from primary sources and quoting from secondary references such as a book or a review article should be avoided. References should include the title of the article, the journal where study appears, volume and page numbers, and date of report or publication. Where appropriate, "unpublished report", its authors and their affiliation should be used. Lesser details can be cross-referenced within the appropriate individual data element.

Only one study should be summarised per Robust Study Summary. In cases where multiple studies are available, separate Robust Study Summaries should be prepared. However, if more than one reference is available describing the available study (such as the original study and published articles of the study results), then it would be appropriate to have one single study summary with multiple references.

**Remark:** This section includes a free text field for general remarks.

Note that the structure and items given in the robust summary templates are intended to provide guidance on the type of information to be included, but do not exactly mirror the corresponding IUCLID subchapter screens. The items provided in the templates either correspond with defined fields in IUCLID or must be entered in IUCLID free text fields. The type of information described in OECD templates under "Remarks" normally must be entered into IUCLID free text fields. The most appropriate free text type should be selected, e.g. "Test Conditions", "Results" etc. Only information that does not fit into a specific free text type should be entered in free text type "Remarks". For additional guidance see the *Guidance for entering data into SIDS Dossiers using the IUCLID Software* in Annex 2.

### 2.4.3.3 Key studies

In general, a key study is the study that has been identified as most suitable to describe an endpoint from the perspective of quality, completeness and representativity of data. When several study results are available on a specific endpoint (maybe using different species or routes of exposure), they can be used together to derive a more sound hazard assessment. However, they can also originate from different periods of time and laboratories, they can be of different quality and can be performed according to different guidelines and so each study's value to the hazard assessment has to be judged individually. Making Robust Study Summaries for all these studies could be unnecessary. The key study concept may be useful to distinguish the studies that need to be summarised in detail from those that do not, thereby reducing the workload.

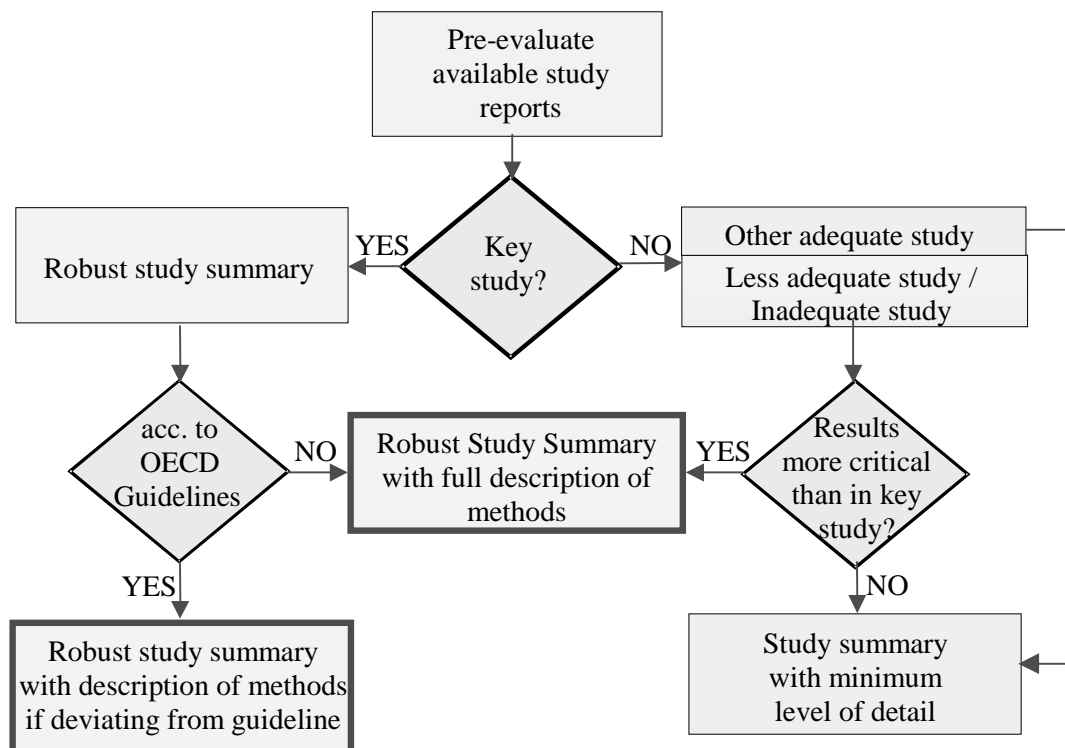
#### *Criteria for key studies*

The prerequisites for a key study concept related to toxicological and ecotoxicological studies are that it:

- a) is in accordance with the principles laid down in the relevant Test-Guidelines;
- b) is a tiered, transparent approach that ensures that at least one reliable study is defined as key study for each SIDS element;
- c) has a certain flexibility to allow for special data conditions and hazard assessment requirements following consultations with a SIDS Contact Point.

Figure 2.1 gives a decision tree for defining the level of detail for reporting key studies and non-key studies.

**Fig. 2.1.-**Decision tree for defining the level of detail for reporting of key and non-key studies



All available significant studies should be referenced in the dossier. For non-key, less substantive studies, summaries need not be as robust for weight of evidence support. A study summary with a minimum level of detail is sufficient. For studies that are flawed, but indicate critical results, Robust Study Summaries highlighting the weaknesses of the studies need to be elaborated. These considerations apply primarily to SIDS elements, but should also be made for other endpoints.

#### *Toxicological studies*

If there are several reliable tests (for example, for acute oral toxicity testing on the same species), the most appropriate test should be summarised as key study. The key study for a specific endpoint is normally defined as the study, which results in the lowest no-effect value (below which no effects were seen for that endpoint in that or any other study) or the lowest effect dose (e.g. LD<sub>50</sub> or LC<sub>50</sub>) (indicating highest toxicity) and the characteristic signs of toxicity for the substance in the relevant species. The most sensitive species should normally be used, except in those cases where evidence is available that the given effect(s) are species specific and are not relevant for human health evaluation.

A short summary (including the main results and an indication of the reliability) of all studies performed should be provided in the SIDS Dossier. The key study should be selected and summarised in greater detail according to the Robust Summary Templates. If there are several reliable studies based on different test guidelines on the same endpoint, the key study should be selected from the method with the highest sensitivity (for example, a Magnusson and Kligman test instead of a Buehler test). It might be

necessary for several studies to be considered as key studies for the same endpoint (for example, when data is available on several species or different routes of exposure or if different results are observed in valid tests). Several Robust Study Summaries may be required for genotoxicity as different types of studies evaluate different genotoxicity endpoints. In any case, Robust Study Summaries should be elaborated for all studies with positive findings for the endpoints of mutagenicity, teratogenicity unless they give only supporting evidence to selected key studies with positive findings. Also for irritation, sensitisation and carcinogenicity, which are not SIDS elements, Robust Study Summaries should be elaborated for positive findings unless they give only supporting evidence to selected key studies with positive findings.

#### *Ecotoxicological studies*

A short summary (including the main results and an indication of the reliability) of all studies performed should be provided in the SIDS Dossier. The key study should be selected and summarised in greater detail according to the Robust Study Templates. If there are several reliable studies based on different test guidelines on the same endpoint, the key study should be selected from the method with the highest sensitivity. It might be necessary for several studies to be considered as key studies for the same endpoint (for example, when data is available on several species or if different results are observed in valid tests). The environmental hazard assessment will focus on the most critical value for each endpoint. For example when more than one LC/EC 50 value is available, the lowest result from a valid study is chosen and a Robust Study Summary is developed for the corresponding study. Robust Study Summaries need also be elaborated for studies giving more critical results but which are considered inadequate or invalid. For endpoints with many available data and for which a conclusion is taken on a weight of evidence approach (e.g. ready biodegradation) it might be necessary to produce Robust Study Summaries for all available test results.