EPA United States Environmental Protection Agency

Office of Pollution Prevention and Toxics

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HPV Challenge Program

3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide)

In order to assure harmonized responses from Member countries and to ensure consistency on requests for further testing, this guidance document (SIDS guide) has been developed. This documents show data requirements and Test guidelines to be used on each data element.

Note: Figures in [ ] correspond to the data elements in the HEDSET and in the Revised OECD HPV Form 1.

1. GENERAL INFORMATION

[1.01 A.] CAS-number

· Should always be stated.

[1.01 C.] Name of the Substance

· Should always be stated.
· Use the name supplied by the OECD.

[1.01 D.] CAS-descriptor

· Should be stated where applicable for complex chemicals.

[1.01 G.] Structural Formula

· Should be given where possible.

[1.5] Quantity

· Should be given where possible.
· Information on production and/or import levels should be provided as tonnes per annum (or ranges, e.g., 100-500 tonnes, see Annex 6 to Section 2.5) per country and the date for which those figures or ranges apply should be given.

[1.7] Use Pattern

· Should be given where possible.
· Data on use pattern should be given by assigning main types according to their exposure relevance, industrial

categories and use categories. Detailed explanation on categories is given in Annex to Section 2.6 and the HEDSET explanatory note.

· If the chemical is present in consumer products as marketed, details should be mentioned on;
- function of the products (e.g. detergent etc.),
- weight fraction of the chemical in products and
- physical state of products as marketed (e.g. aerosol, powder or liquid))

[1.9] Sources of Exposure

· Should be given where possible.
· Describe sources of potential human or environmental exposure including emission data if available for all phases of the life cycle of the chemical including manufacturing and user areas.
· For environmental exposure, indicate the production process briefly, number of sites of manufacture and the basis for concluding that the process is "closed" if applicable.
· Indication of measured exposure levels can be mentioned here. Any information that will help to focus the assessment of exposure can be mentioned, if available

2. PHYSICAL-CHEMICAL DATA

[2.1] Melting Point

· Should always be stated for substances other than gases (and liquids whose melting point is lower than approximately 0°C.) Temperature of decomposition is acceptable.
· OECD Test Guideline 102

[2.2] Boiling Point

· Should always be stated for substances other than gases or solids and liquids which either boil above 300°C or decompose before boiling (in which cases estimates based on vapour pressure or the boiling point under reduced pressure are necessary). Temperature of decomposition is acceptable.
· OECD Test Guideline 103

[2.3] Density (Relative Density)

· Where applicable, indicate the relative density of the substance. This property is generally more important for inorganic chemicals.
· OECD Test Guideline 109

[2.4] Vapour Pressure

· Should always be stated.
· Calculations which indicate that the value is probably less than 10^{-5}kPa at 25°C, could preclude the need for testing.
· If a boiling point cannot be quoted due to decomposition or the melting point is above 360°C, it may not be necessary to conduct this test. If a melting point is <360°C but >200°C, a limit value based on measurement or a recognised calculation method is acceptable.
· This test is not essential for chemicals with a boiling point of <30°C.
· OECD Test Guideline 104

[2.5] Partition Coefficient (n-Octanol/water)

· Should always be stated.
· Even for those substances which are extremely soluble/insoluble in either phase, an attempt should be made to provide a limit value (if necessary based on the individual solubilities in n-Octanol and water). It is recognised that for surface active substances, the measured result may only be approximate.
· The MedChem database is a good source of data.
· If the test cannot be performed, a calculated value for Log Pow should be provided. However it should be noted that calculated values which are higher than 6 are, in general, not reliable.
· For calculation of Pow, see e.g.:

- C. Hansch, A.J. Leo in Substituent Constants for Correlation Analysis in Chemistry and Biology, John Wiley, New York, 1979.
- W.J. Lyman, W.J. Reehl, D.H. Rosenblatt (ed.), Handbook of Chemical Property Estimation Methods, McGraw-Hill, New York, 1983.
- Annex to OECD Test Guideline 117.
- Application of Structure Activity Relationships to the Estimation of Properties Important in Exposure Assessment, OECD Environment Monograph No.67, 1993.

· OECD Test Guidelines 107, 117

[2.6. A.] Water Solubility

· Should always be stated, including gases if necessary, excluding volatile substances and substances unstable in water.
· Determinations should be made at or near 20°C. If solubility/temperature dependence is>3% per °C, further measurements should be made at 10°C above and below the initially chosen temperature. If the substance is "insoluble" in water, the detection limit of the analytical method should be indicated.
· OECD Test Guideline 105

[2.6.B.] pH Value and pKa Value

· Where applicable, enter values for the dissociation constant(s)and the conditions under which they were measured.
· Dissociation constants are particularly important for acids, bases and inorganic chemicals (and are normally known calculated or measured).
· OECD Test Guideline 112

[2.12] Oxidation-Reduction Potential

· Where applicable, indicate the redox potential and the conditions under which it was measured. This property is generally more important for inorganic chemicals.

[2.13 A.] Adsorption/ Desorption to Soil

· Where applicable, indicate the adsorption/ desorption to soil and conditions under which it was measured.
· This property is particularly important for inorganic chemicals in cases where Log Pow is not useful in view of the expected properties of the chemicals.
· OECD Test Guideline 106

3. ENVIRONMENTAL FATE AND PATHWAYS

[3.1.1] Photodegradation

· For photodegradation, an estimation is generally sufficient.
· Estimation of photodegradability (and hydrolysis) can be based on reference documents, e.g., "An Assessment of Test Methods for Photodegradation of Chemicals in the Environment" (ECETOC Technical Report No.3) and "Handbook of Chemical Property Estimation Methods" (W.J. Lyman, W.J. Reehl, D.H. Rosenblatt (ed.), Handbook

of Chemical Property Estimation Methods, McGraw-Hill, New York, 1983.)
· OECD Test Guideline 113

[3.1.2] Stability in Water (Hydrolysis)

· Testing is generally required for hydrolysis unless adequate data is already available. But consideration should be given to the possibility of using estimation methods.
· Additional testing may be required for hydrolysis even if data have been supplied, given consideration to:

- choice of test protocol;
- quality of data.

· When possible, the products of hydrolysis should be identified.
· OECD Test Guideline 111

[3.2] Monitoring Data (Environment)

· Where available, indicate an overview of monitoring data in the environment with specifications of conditions.

[3.3] Transport and Distribution between Environmental Compartments including Estimated Environmental Concentrations and Distribution Pathways

· Environmental concentration and important fate and between pathways based on simple models, e.g., those in the "Guidance for Initial Assessment of Environmental Exposure" and "Compendium of Environmental Exposure Assessment Methods for Chemicals" (OECD Environment Monograph No.27) etc. should be described.
· In particular calculation of distribution of a chemical between environmental compartments by a Fugacity Level I model should be provided. (The diskettes which accommodate global reference model (FUGMOD) and other national models which have been distributed by the Secretariat can be used for this purpose.)

[3.5] Biodegradation

· Testing is generally required, other than for gases, unless adequate data is already available.
· Additional testing may be required even if data have been supplied, given consideration to:

- choice of test protocol;

- quality of data.

· OECD Test Guideline 301A-301F
· The feasibility of each OECD Test Guideline (301A-301F) may be dependent on the physical-chemical properties (e.g., stability in water), and the structure of the test substance.

4. ECOTOXICITY

· Where aquatic tests are carried out on poorly soluble substances at nominal concentration above the solubility limit in the test medium, and no mortalities or effects are observed, then the LC50, EC50 and NOEC should be indicated as being above the stated solubility limit in the test medium.
· For poorly soluble substances, it should also be clearly stated whether solvents were used to enhance the solubility. Testing at the solubility limit, without solvent, is preferred.
(*) For substances which decompose in water, LC_{50}, EC_{50} and NOEC should be expressed in terms of the nominal concentration of the tested substance.

[4.1] Acute/Prolonged Toxicity to Fish

· Testing is generally required if no adequate data is already available.
· Additional testing may be required even if data have been supplied, given consideration to:

- results from testing and calculations;
- quality of data.

· OECD Test Guideline 203 (*)

[4.2.A] Acute Toxicity to Aquatic Invertebrates (*Daphnia*)

· Acute testing is generally required if no adequate data is already available.
· Additional testing may be required even if data have been supplied, given consideration to quality of data.
· OECD Test Guideline 202, Part 1 (*)

[4.3] Toxicity to Aquatic plants e.g. Algae

· Testing is generally required if no adequate data is already available.
· Additional testing may be required even if data have been supplied, given consideration to quality of data.

· OECD Test Guideline 201 (*)

[4.5.2] Chronic Toxicity to Aquatic Invertebrates (Daphnia)

· Chronic testing will be required if there is concern about possible long-term effects in the aquatic environment.
· OECD Test Guideline 202, Part 2 (*)

[4.6] Toxicity to Terrestrial Organisms

· If significant exposure is expected in the terrestrial environment compartment, appropriate terrestrial toxicity tests should be performed.
· In determining whether significant exposure may be expected in the terrestrial environment, the following should be considered:

- the chemical has a potential for reaching the terrestrial environment based on use and transport patterns and disposal practices taking into account all phases of the life cycle combined with;
- physical-chemical properties indicate the compound may be persistent, has a potential to bioaccumulate or a major portion may partition to the soil; or
- measured data indicate residues in soil, waste water sludge or groundwater.

· In considering which terrestrial testing should be undertaken, it should be taken into account that studies 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 cross media considerations.
· Initially, a test should be performed on terrestrial invertebrates and/or plants. The results of other tests may indicate the need for avian toxicity tests.
· OECD Test Guideline 205-208 (*)

- 205: Avian Dietary Toxicity Test
- 206: Avian Reproduction Test
- 207: Earthworms Acute Toxicity Test

· The artificial soil test is preferred because the paper contact test is not truly representative of the natural habitat.

- 208: Terrestrial Plants, Growth Test

5. TOXICITY

[5.1] Acute Toxicity

· Testing is generally required if no adequate data is already available. Consideration should be given to the possibility of using data from analogues or repeated dose toxicity studies on the same substance.
· Additional testing may be required even if data have been supplied, given consideration to:

- test species;
- route of exposure;
- quality of data.

· The rat is the preferred species (oral and inhalation). For dermal tests, the rat, rabbit or guinea pig are preferred species.
· All substances, except gases and vapours, should be tested by the oral route. Dependent upon the physical-chemical properties of the substance and the most important route of human exposure, the dermal or the inhalation route could also be considered. Gases should be tested by the inhalation route alone.
· OECD Test Guideline 401-403, 420

[5.4] Repeated dose Toxicity

· Testing is generally required if no adequate data is already available.
· Additional testing may be required even if data have been supplied, given consideration to:

- test species;
- route of exposure;
- duration of exposure;
- quality of data.

· The rat is the preferred species but consideration should be given to the species used in the acute test. Oral, dermal and inhalation routes should be considered. The oral route is normally preferred. The appropriate route should be selected dependent on physical-chemical properties of the substance, the results of the acute toxicity tests and the most important route of human exposure.
· OECD Test Guideline 407, 410 and 412
· The "Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test" (OECD Test Guideline 422) is also acceptable.

[5.5] [5.6] Genetic Toxicity in vitro and in vivo

· Testing is generally required if no adequate data is already available.
· Additional testing may be required even if data have been supplied, given consideration to:

- test organism, strain and/or cell system;
- if metabolic activation has been used;
- quality of data.

· Two different endpoints should be tested: gene mutation and chromosomal aberration. These endpoints may be evaluated by using the following tests:
- Gene mutation in prokaryotic cells, should be performed preferably in Salmonella typhimurium (OECD Test Guideline 471). The chemical class of the test substance may determine which test organism and whether modified procedures may be needed. The test should be carried out with and without metabolic activation.
- Chromosomal aberration in mammalian cells grown in vitro (OECD Test Guideline 473) or in vivo methods such as the micronucleus test or metaphase analysis of bone marrow cells (OECD Test Guidelines 474, 475). 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.

[5.7] Toxicity to Reproduction

· Testing is generally required if no adequate data is already available.
· Additional testing may be required even if data have been supplied, given consideration to:

- test species;
- duration of exposure;
- quality of data.

· For the reproduction toxicity endpoint,
- when a 90-day repeated dose study is available and is sufficiently documented with respect to studying effects on the reproductive organs and a developmental study is available, the requirements for the reproduction toxicity endpoint are satisfied;
- when either a 90-day or 28-day repeated-dose study is the only repeated dose study available, it is recommended that the reproduction/developmental toxicity screening test (e.g.

OECD Test Guideline 421) be carried out in order to satisfy the requirements for the reproduction toxicity endpoint; and
- when a 90-day repeated dose study is available and demonstrates no effect on reproductive organs, in particular the testes, then a developmental study (e.g. OECD Test Guidelines 414) can be considered as an adequate test to complete information on reproduction/developmental effect.
· OECD Test Guideline 415 - 416. The screening tests [OECD Test Guideline 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, (for when repeated dose toxicity is not available) and OECD Test Guideline 421: Reproduction/Developmental Toxicity Screening Test (for when repeated dose toxicity is available)] are also acceptable.

[5.8] Developmental Toxicity/Teratogenicity

· Endpoint of developmental toxicity is generally required if no adequate data is already available. See Toxicity to Reproduction.
· OECD Test Guideline 414

[5.11] Experiences with Human Exposure (Work Place Exposure)

· Information on work place exposure such as;

- concentration of chemicals in the workplace (manufacturing, maintenance and professional use) and indoor environment,
- number of workers (in range or situations including manufacture, maintenance and use),
- frequency, duration and level of exposure should be mentioned if available.

· Effects of accidental or occupational exposure, epidemiological and clinical studies, case reports, etc. can be described.

3.5 Considerations Concerning the Adequacy of Data in the SIDS ***

General

1. Each National SIDS Contact Point must have the opportunity to evaluate the quality of data in the SIDS for chemicals with complete studies available for which they are responsible as a Sponsor country.
2. OECD Test Guidelines and GLP Principles are generally used to produce studies of acceptable quality. However, data may be considered

adequate for the purposes of screening even if not totally acceptable by international standards (e.g. OECD Test Guidelines, GLP Principles). This is best determined by expert judgement on a case-by-case basis.
3. It may not be necessary to conduct certain studies in cases when:

· other studies, for example on analogues, are available and the results are consistent - e.g., acute toxicity studies, biodegradation studies;
· there are other relevant studies or calculations available, and the results are consistent, which diminishes the need for retesting; and/or
· an approximate value is adequate for screening purposes, e.g. acute toxicity studies.

4. If studies have been carried out according to guidelines other than those of the OECD, these test methods should be clearly described. Also if calculated data are reported, the method of calculation and its justification should be described.

5. In the same way, if studies have not been carried out under the OECD GLP Principles, an explanation for not doing so must be provided.

6. If some SIDS data are inadequate or missing, there will be a bias for testing unless a rationale for not testing is provided and is accepted in the international context. Again, bearing in mind animal welfare considerations, internationally acceptable methods of in vitro testing should be considered as a first line of approach.

7. Studies should be referenced as clearly as possible so that, when data are prepared for transfer to IRPTC and IPCS, they can be properly identified and coded.

Physical-chemical Data

8. Physical-chemical data for boiling point and melting point when taken from reliable references (i.e. from handbooks) rather than taken from actual test reports can generally be accepted because there is good confidence in these data based on experience. Information on related compounds may be useful in affirming physical-chemical parameters.

9. For vapour pressure, octanol/water partition coefficients (Pow) and water solubility studies, more scrutiny may be required as such data are more critical to the initial assessment of potential hazards, e.g. bioaccumulation. In particular, calculated values of log Pow are not reliable if greater than 6. The American MedChem database could be used as a good source of data for these endpoints.

10. Key information which affects the value of physical-chemical properties such as temperature and methods used must be provided.

Environmental Fate Data

11. As for biodegradation data on a chemical, the most important issue at the level of the SIDS is whether a compound is readily biodegradable or not. Therefore, in any ready biodegradability test, the following figures should be provided:

- the number of micro-organisms present;
- the time window for 10 per cent degradation; and
- the test results at the end of the test.

It is necessary to present these data for tests which are comparable with ready biodegradation tests. Other biodegradation data that are available, especially data obtained using natural media such as soil or river water, should also be included in the SIDS dossier.

12. Distribution of a chemical between environmental compartments can be calculated by the Fugacity Level I Model in the FUGMOD computer program, which has been distributed by the OECD Secretariat and can be obtained from SIDS Contact Points. Primarily partition coefficients such as soil/water Koc, Henry's constant and BCF's are required for inputting into the fugacity model when it is used.

Ecotoxicity and Toxicity Data

13. If any of the required ecotoxicity or toxicity studies are lacking, consideration may be given to waiving some testing endpoints where there are adequate data for closely related analogues. This should be closely scrutinised on a case-by-case basis.

14. For a proper evaluation of ecotoxicity and toxicity studies, detailed information should be reported in addition to those explicitly required in the Revised OECD HPV Form 1 or the HEDSET. Lack of detail in reporting toxicity or ecotoxicity data does not automatically lead to the need to re-test, but this will delay a decision on the acceptability and adequacy of toxicity and ecotoxicity studies mentioned in the SIDS Dossiers. Availability of detailed information for all tests make the review by other countries much easier and more efficient. Examples of details on the information on the aquatic toxicity tests which could be reported, if available, recommended by the Netherlands and the US respectively, are attached as an Annex to this section.

15. If the data presented from studies not fully in compliance with GLP Principles and/or not conducted according to internationally acceptable test guidelines suggest a very low concern for the desired endpoints, i.e. a high and acceptable NOEL, then the test may be considered adequate for screening purposes.

***The 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).

Annex

Information to be Used in the Evaluation of Aquatic Toxicity Test Results, if available

1. Items and Contents Recommended by the Netherlands

A. Organism
B. Method
C. Test-system: static; semi-static; continuous flow
D. Test result:

-- fish: 24 + 48 + 72 + 96 hour
-- daphnia/acute: 24 + 48 hour
-- algae: 24-72 hr: EC50 + NOEC + parameters used; biomass or growth rate
-- daphnia/chronic: NOEC, LC50(21d), EC50(21d) (in cases where chronic data are needed)

E. Purity of test compound
F. Whether analysis has been carried out and if so:

-- Is the result based on the nominal or measured concentration?
-- If the result is based on the measured concentration, an indication of the discrepancies should be given.

G. Additional information for special compounds:
(This information also is required for biodegradation tests.)

-- volatile substance: was an open or closed system used?
-- insoluble substance: if a solvent is used, how much has been added and has a solvent control been carried out?

2. Items and Contents Recommended by the US

A. Organism:
Age, mean length and mean weight, as appropriate; loading.

B. Test System:
For semi-static, time period between renewal; for continuous flow, number of replacements per day.

C. Fish Test Result:
24, 48, 72 and 96 hr results; discriminate between intrinsic (chemical) toxicity and physical toxicity; sub-lethal effects observed.

D. Daphnia Test Result (acute):
24 and 48 hr result; discriminate between intrinsic (chemical) toxicity and physical toxicity; sub-lethal effects observed.

E. Algae Test Result:
24-72 hr (96 hr EC50, if available); NOEC and LOEC; parameter used (biomass or growth rate).

F. Analytical Method:
Detection limit, mean per cent recovery, table of nominal concentrations and measured concentrations withtime interval(s) indicated, mean measured concentrations, statement as to how concentrations below the detection limit were handled in the calculation of mean measured concentrations; concentration values should be reported as "100% active ingredient."

G. Dilution Water:
Source, hardness, pH, total organic carbon (TOC), total suspended solids (TSS).

H. Algae Growth Medium:
Composition; final concentrations of nutrients in medium; TOC; hardness.

I. pH of Test Solution:
pH of test solution at t=0 hr and 48 hr or 96 hr as appropriate.

J. Purity:
Impurities; physical state.

K. Aeration:
Was aeration used during test; if yes, how much and by what method?

L. Volatile:
For closed systems, presence of head space; size of any head space; modifications of closed test system relative to open test system, e.g. adjustments in algal growth medium of bicarbonate concentration.

M. Stock Solution Preparation:

> (1) If a stock solution was prepared, this procedure must be carefully evaluated using considerations such as the following: check all calculations from test material to stock solution; concentration to treatment concentrations; indicate clearly if stock solution concentration was based on test material "as is" or on 100 percent active ingredients; solvents or carriers used and their possible effects; concentration of solvents or carriers used; pH of stock

solution; pH adjustment, if any; time between stock solution preparation and addition of organisms to exposure vessels; observations of physical appearance of stock solution: clear, milky dispersions as observed for detergents and charged polymers, dispersed solids, precipitate, oily slick or phase separation, etc.; if precipitates are present, how were they handled: mixed and distributed to exposure vessels of filtered out; if filtered out, what type of filter, were all solids filtered or only part of solids; was only the water soluble fraction (WSF) removed from the stock solution; methods used to dissolve test material: sonication (how long), mixing time heating, etc.

(2) If no stock solution was prepared, the direct dilution of test material was employed. What was the time between direct dilution of the test material to the exposure vessel and the addition of organisms?

[Note: Not all of these points are of equal relevance to the evaluation of tests, depending on the nature of the specific chemical. Guidance could be developed as to when certain information is critical to interpreting study results on a given class of chemicals in later phases of the HPV programme.]

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