MANUAL FOR INVESTIGATION OF HPV CHEMICALS

CHAPTER 3: DATA EVALUATION

3.1 Guidance for Determining the Quality of Data for the SIDS Dossiers: (Reliability, relevance and adequacy)[1]

3.1.1 Introduction

1. There are approx. 5000 chemicals on the OECD List of High Production Volume Chemicals (last updated in 2004). The OECD HPV Chemicals Programme provides for an initial assessment of the potential human health and environmental hazards of a chemical.

2. The first step in the investigation of a HPV chemical is to collect and carry out a review to ensure that there is sufficient good quality information on each of the elements that make up the Screening Information Data Set (SIDS). This is necessary before deciding if additional testing is required for any given HPV chemical.

3. The purpose of this document is to provide basic guidance to industry, governments, and other interested parties on the first steps of a process, which ultimately ends in decisions about, whether existing data are sufficient to fill a SIDS data element.

4. The document is not intended to present all possible approaches which can be used to assess data quality but presents two tools, one already used by industry and another proposed by governments which is a more criteria driven approach for compiling and assessing the completeness of Screening Information Data Sets (SIDS) on HPV chemicals.

3.1.2 The Screening Information Data Set (SIDS)

5. The SIDS is used for making an initial hazard assessment on HPV chemicals and provides the basis for conclusions on potential human health and environmental hazards and recommendations on the need for further work.

6. In developing the SIDS, the OECD made maximum use of OECD Test Guidelines to establish the recommended test methods for the generation of new data on SIDS elements. Use of OECD Test Guidelines and OECD Principles of Good Laboratory Practice ensures that any newly generated test data is accepted under the OECD system of Mutual Acceptance of Data [see C(81)30 (Final)]. Data generated under this system is accepted between countries for assessment purposes without the need for repeat testing.

7. Consideration of all available existing information on an HPV chemical is important because, if it is judged to be of sufficient quality, there is no need for additional testing for that SIDS element, resulting in savings in resources, such as time, costs and laboratory animals.

3.1.3 The quality of existing data

8. The process of determining the quality of existing data takes into consideration three aspects - adequacy, reliability and relevance of the available information to describe a given SIDS element.

[1] This document was prepared by the OECD Secretariat based on the agreements reached in the OECD Existing Chemicals Programme up to December 2005.

These terms were defined by Klimisch et al. (1997) along the following lines:

- **Reliability** - evaluating the inherent quality of a test report or publication relating to preferably standardised methodology and the way the experimental procedure and results are described to give evidence of the clarity and plausibility of the findings;

- **Relevance** - covering the extent to which data and tests are appropriate for a particular hazard identification or risk characterisation; and

- **Adequacy** - defining the usefulness of data for hazard/risk assessment purposes. When there is more than one study for each SIDS element, the greatest weight is attached to the study that is the most reliable and relevant. Robust study summaries are prepared for the highest quality or "key"studies.

9. The guidance deals primarily with determining the reliability of data. This essentially relates to how the study was carried out. This information is needed to enable robust study summaries to be prepared and before relevancy and adequacy can be considered.

10. Careful consideration must be made of the quality of the study, the method, the reporting of the results, the conclusions drawn and the results in order to complete a robust study summary.

11. There are several reasons why existing study data may be of variable quality. Klimisch et al, 1997, have suggested the following:

- the use of different test guidelines (compared with today's standards);
- the inability to characterize the test substance properly (in terms of purity, physical characteristics, etc.);
- the use of crude techniques/procedures which have since become refined; and
- the fact that certain information may have not been recorded (or possibly even measured) for a given endpoint, but that it has since been recognized as being important.

12. The first step in assessing whether data gaps exist for an HPV chemical is to conduct a literature search and search of company records, as appropriate. The existing data identified in the search should then be reviewed to determine whether additional testing is necessary.

13. The identification of the need for additional testing may be considered at any stage of the data collection and review process including:

a) the initial determination of the quality of the data;
b) the preparation of robust study summary(ies) for most relevant and reliable study(ies) for each SIDS element; and
c) development of a test plan, if necessary.

14. In some cases the type of substance under investigation will result in the recommended SIDS test for a particular element being difficult or inappropriate to carry out, e.g. chemicals which are unstable in abiotic or biotic systems, chemicals with known explosive/flammable properties or volatile substances. In such cases the relevance of the study may be questionable.

15. Each study essentially will require a case by case consideration and for these reasons a quick look at the reliability of the studies may save time later when relevance and adequacy are considered. At least a minimal amount of information on the reliability of a given study needs to be known before proceeding to determine its relevance and adequacy for SIDS initial assessment purposes and before proceeding to

develop a robust study summary. The following guidance therefore provides two consistent approaches, which may be used as an initial or first screen.

3.1.4 Initial screen for reliability

16. The reliability of the data is a key initial consideration, which can be done relatively quickly to filter out unreliable studies and focus further resources on those considered most reliable. Without knowledge of how the study has been conducted all other considerations may be irrelevant. Two approaches have been proposed to assist the initial screening of study reports to set aside unreliable study data. Both are compatible and may be used either alone or together by a person compiling a SIDS Dossier and considering data quality.

17. One approach is that developed by **Klimisch et al. (1997)**. This approach was developed as a scoring system for reliability, particularly for ecotoxicology and health studies; however it may be extended to physicochemical and environmental fate and pathway studies. The other approach was developed in 1998 as part of the **US EPA HPV Challenge Programme**.

18. Klimisch et al. (1997), developed a scoring system which can be used to categorize the reliability of a study as follows:

> **1 = reliable without restrictions**: "studies or data...generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline...or in which all parameters described are closely related/comparable to a guideline method."
>
> **2 = reliable with restrictions:** "studies or data...(mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable."
>
> **3 = not reliable**: "studies or data...in which there were interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., unphysiologic pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment."
>
> **4 = not assignable**: "studies or data....which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.)."

19. The use of Klimisch codes provides a useful tool for organising the studies for further review. E.g. it would allow the person reviewing the studies to focus on the most highly reliable study first to allow time to be devoted later to consider relevance and adequacy of the reliable studies only. Studies, which failed to meet essential criteria for reliability, would be set aside at the beginning. Provision has been made to add Klimisch scores into the information on specific studies in the SIDS Dossier [see Annex 1 to the Guidance for Developing Robust Study Summaries for SIDS Dossiers]. .

20. The second approach developed by the US EPA approach provides more information than the Klimisch system by describing the key reliability criteria for each type of data making up the SIDS Dossier (Table 1). These criteria address the overall scientific integrity and validity of the information in a study, i.e. reliability. This approach is consistent with the Klimisch approach - any study, which does not meet

the criteria in Table 1, would also not be assignable under the Klimisch system. Such studies may be however be considered later as supplementary information to the overall assessment of a particular SIDS element particularly if there is no single key study.

3.1.5 Determination of relevance and adequacy

21. The use of sound scientific judgment is the most important principle in considering relevance and adequacy. The studies that have passed the initial screen should be considered using the guidance used for assessing SIDS data elements and compiling robust study summaries [see Guidance for Developing Robust Study Summaries for SIDS Dossiers.]. These documents highlight aspects of the information that must be available in order for the study to be considered relevant and adequate for the SIDS initial assessment. At this stage it is expected that one or more key studies that best represent a particular SIDS element and whether robust study summaries can be prepared, will be identified.

22. The more detailed assessment of relevance and adequacy is very much related to preparing the SIDS Dossier (including robust study summaries, as appropriate). It can therefore be regarded as a second tier consideration.

3.1.6 Weight-of-the-Evidence Analysis

23. The use of tools for identifying reliable and relevant and adequate data to prepare robust study summaries helps to ensure that high quality data is used in the OECD HPV Chemicals Programme. They do not however remove the need for a weight-of-evidence analysis approach during the assessment of this data.

24. Similarly the assignment of Klimisch Codes for data reliability does not necessary mean that any extra weight should be given to these studies in the overall initial assessment, as there may be information from other studies on other elements which have an influence. Documentation prepared for the HPV Chemicals Programme will need to be explicit on the criteria, which have been applied to assess quality, rather than simply referencing a score.

25. Some HPV chemicals have been tested in a variety of studies that are beyond SIDS (e.g., neurotoxicity, fish chronic toxicity test, etc.), whereas the tests for the SIDS endpoint have not been carried out. In such cases, if a rationale can be presented to show that such non-SIDS tests adequately describe the SIDS element of concern, a new test for that particular endpoint may not be necessary.

26. Because of the nature of existing data, it is reasonable to expect that there will be some cases (for a given SIDS element) in which several studies - some of which may not have passed the initial screen may be collectively used to fill the element, thereby avoiding additional testing.

27. The pooling of several studies, one or more of which may be inadequate, to satisfy a specific SIDS element is another way that a weight-of-the-evidence analysis can be made. For example, there may be several repeated dose studies available on a particular chemical, none of which would be acceptable by itself due to some deficiency (i.e., low number of test animals/dose group, only one dose group in addition to control group, change in dose amount or frequency during the course of the study, etc.). Collectively, however, the different studies show effects in the same target organ at approximately the same dose and time. This could satisfy the repeated dose toxicity data element for SIDS.

Table 1: Initial Screening Criteria for data reliability by type of SIDS information items

Criteria	Required for following SIDS Information Items		
	P/Chem	**Env.Fate**	**Ecotox /Health**
Test Substance Identification (Adequate description of test substance, including chemical purity and identification/quantification of impurities to the extent available).	**X**	**X**	**X**
Temperature	**X**[1]	**X**	**X**
Full Reference/Citation	**X**	**X**	**X**
Controls[2]		**X**	**X**
Statistics With some exceptions (e.g., the *Salmonella*/Ames assays**)**			**X**
Species, strain, number, gender, & age of organism			**X**
Dose/conc. Levels		**X**	**X**
Route/type of exposure[3]			**X**
Duration of exposure		**X**	**X**

Footnotes to Table 1

1. For vapour pressure, octanol/water partition coefficient and water solubility values
2. All studies must have negative controls and some studies (e.g. biodegradation, Salmonella/Ames assay) must also have positive controls. If a vehicle is used in the administration of the test agent, vehicle controls should be established and reported. Exceptions may be allowed for acute mammalian toxicity studies.
3. The route/type of exposure (e.g., oral inhalation. etc for mammalian studies) or test system (static, flow-through, etc for ecotoxicity) must be reported.

3.1.7 Use of secondary data sources for physico-chemical endpoints

28. The primary concern for SIDS endpoints presented in submissions to the OECD HPV Chemicals Programme is that they should be accurate, reliable and valid. It is particularly important that accurate values are established for parameters such as the octanol-water partition coefficient, aqueous solubility and vapour pressure, which are required to predict environmental exposure and interpret ecotoxicity test data.

29. The reliability of data is demonstrated by the preparation of a Robust Study Summary, as detailed in Section 2.4.3. This provides information such as the identity of the test substance, the methodology used to make the measurement and whether this was performed to GLP standards. In order to obtain this information, reference should ideally be made to the primary data source, such as a published paper or test report[2]. Section 2.2.3, on existing SIDS data, states that "…as far as possible, original publications should be retrieved".

30. However, in the case of well-studied chemicals it may be acceptable to use values for physico-chemical parameters obtained from reliable secondary sources such as standard references, which are known to publish 'peer reviewed' data, i.e. the data available in the literature are critically evaluated and an appropriate, reliable value selected. It is appropriate to assign these sources of peer reviewed data a reliability code of (2), 'valid with restrictions', when considering reliability, since it is assumed that a variety of data sources have been consulted and the test methodology and identity of the test substance have been evaluated, and a reliable and representative value for the endpoint selected. Whether such a review process has been conducted should be stated in the introduction to the handbook or contained in the summary information for an on-line database.

31. Useful reference books and data compilations containing peer reviewed physico-chemical data (some of which are listed in Section 2.2.3) include:

- The Merck Index;
- The CRC Handbook of Chemistry and Physics;
- The IUPAC Solubility Data Series;
- Beilstein Database and;
- Illustrated Handbooks of Physical-Chemical Properties and Environmental Fate for Organic Chemicals.

32. Online databases such as the SRC PhysProp Database[3] and HSDB[4] on the TOXNET network are good sources of data and generally provide a reference for the value that they have selected. Because these database sources are usually secondary data sources themselves, the original data source should be checked and referenced rather than directly citing the database (or secondary data source without retrieving it). Databases such as these are valuable resources that should primarily be used as a source to highlight where data are available.

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[2] If the original data source is an 'old' reference it may be necessary to consider the following: (i) If the reference was published more than 20 years ago, then retrieval could require a lot of time or may not be possible; (2) Current GLP standards may not have been followed; and (3) Older publications may not have routinely provided information regarding the test substances, including the purity.

[3] Available on-line at http://esc.syrres.com/interkow/physdemo.htm. These data are also used to populate the 'Experimental Database' in the EPIWIN software suite

[4] Hazardous Substances Data Bank Available on-line via TOXNET at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

33. The issue of 'data recycling' and the potential for degrading the reliability of data for environmental assessment is an issue of growing concern in the scientific community[5] and reinforces the need for the preparation of a Robust Study Summary (RSS) from the primary data source as best practice.

34. When using data solely from secondary sources it is essential to construct a 'weight-of-evidence' approach (see Section 3.1.6) in order to establish that an appropriate value has been selected for the SIDS dataset. It is not normally acceptable to use a single, peer reviewed secondary source with no further supporting evidence. The SIDS Dossier should present values taken from multiple authoritative data sources, such as those detailed above, in addition to supporting data, such as manufacturing data, reliable QSAR predictions[6], and/or data from sources that may not have been peer reviewed, e.g. Vershueren's Handbook on Environmental Data. Values for physico-chemical properties taken from material safety data sheets (MSDSs) and all other company technical data can only be assigned a reliability rating of (4), unassignable, unless detailed information such as the experimental methodology and test substance are provided to enable the preparation of a RSS and an independent evaluation of the study's reliability.

35. When presenting values for physico-chemical parameters such as vapour pressure, Log Kow and water solubility from secondary sources the important factors to detail, if available, are: whether the value has been measured or estimated, the method of experimental determination or estimation[7]; the temperature at which the measurement/estimation was made and; a full reference/citation. If this is not clear in a handbook or data compilation whether a value has been determined experimentally or estimated then reference should be made to the primary source.

36. Some initial comments on the most common data sources for physico-chemical data are given in Table 2 below. However, it must be emphasised that it is difficult to draw general conclusions regarding the reliability of each data source for an individual parameter and reviewers should make every effort to ensure that the test substance identity, test method and result are reliable, in accordance with Chapters 2 and 3.

Table 2: Common sources for physico-chemical data

Source of physico-chemical data	Comments
Merck Index	Physical data are cited as found in the literature. When several alternate data values appear in the literature, the data is evaluated and representative selections are made; values are then reported with the corresponding source.
Hawley's Condensed Chemical Dictionary	This is a compendium of physical data that are taken to be 'reliable'; "where entries are incomplete, it may be presumed that no reliable data were provided by the reference system utilised". [References for values are not provided]

[5] See Renner R (2002) The Kow Controversy. Environmental, Science and Technology, v36, no. 21, pp. 411A-413A

[6] It should be demonstrated that the QSAR used to estimate a value is appropriate for the type of chemical under consideration (see Section 3.3). If the estimate generated by a QSAR calculation is considerably different to measured value(s) there should be some discussion of the difference, including whether the QSAR applied was appropriate or if the prediction is within the established/validated domain for the model that is being used.

[7] It is important that the methodology employed is appropriate to the particular test substance under consideration.

CRC Handbook of Chemistry and Physics	Data for physical constants have been taken from many sources, including both compilations and the primary literature. Where conflicts were found, the value deemed most reliable was chosen. [Reference sources are provided for selected properties such as solubility and Log Kow; these references are generally authoritative data compilations]
IUPAC Solubility Data Series	The Solubility Data Series is a project of the International Union of Pure and Applied Chemistry (IUPAC). Publication of the series began in 1979, its goal being to present a comprehensive and critical compilation of data on solubilities in all physical systems, including gases, liquids and solids.
Beilstein Database[8]	Beilstein organic substance records contain the critically reviewed and evaluated documents from the Beilstein Handbook of Chemistry as well as data from 176 leading journals in organic chemistry covering the period 1779 to present. [An exhaustive list of values and primary references are provided]
Illustrated Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals (Mackay et al)	Physical properties such as melting and boiling point and density are obtained from commonly used handbooks. Other properties such as solubility, vapour pressure, Log Kow have been obtained from primary reference sources and handbooks. A range of referenced values are reported for each of these properties. Data have been evaluated and a selected 'best value' is given for each property and used in calculations of environmental distribution.
SRC PhysProp Database/ EPIWIN Experimental Database	For compounds with abundant data, values have been taken from databases that had already evaluated the data and selected a reliable value. For compounds with less data, values are selected based on a number of factors including the reliability of the source and details of the experimental methodology. [References are provided for all values, except those for melting point and boiling point, and it is clearly indicated whether values are experimental or estimated]
Yaws Chemical Properties Handbook	"Experimental and estimated values are provided in the compilation based on data source publications for organic compounds" [This handbook provides a list of primary references for each property but they are not assigned to particular values or compounds. It is, however, indicated whether data were determined experimentally or estimated]

[8] CrossFire Beilstein, Licensed by MDL Information Systems GmbH

HSDB on TOXNET	HSDB is peer-reviewed by the Scientific Review Panel (SRP), a committee of experts in the major subject areas within the data bank's scope. All data are referenced and derived from a core set of handbooks, government documents, technical reports and selected primary journal literature".
The Pesticide Manual (currently edited by C Tomlin and previously by CR Worthing).	The introduction to this book (12th Edition) and the discussion of the entries provides no indication that the data has been 'peer reviewed'. There is a brief discussion of vapour pressure (as an example phys-chem property) and it is stated that if there are conflicting values available then the lowest is chosen. A significant proportion of the data is provided directly by manufacturers and is therefore unlikely to have been subject to 'peer review'.
Sax's Dangerous Properties of Industrial Materials	The preface and introduction to this book (10th Edition) provide no indication that the physico-chemical data has been 'peer reviewed'. Physical properties are selected to be useful in evaluating the hazard of a material and designing its proper storage and use procedures. [References for values are not provided]
Bretherick's Handbook of Chemical Reactive Hazards	Several different sources are used. These include primary sources (generally specialist safety journals but also includes general chemical literature), secondary sources (selecting only reactive hazard data) and the direct reporting of incidents to the editors by readers. Full references are given where available. The introduction gives details of the scope and coverage.
Lange's Handbook of Chemistry	The preface to this book states that "every effort has been made to select the most useful and reliable information and to record it with accuracy" but no references are provided for the data presented and there are no indication as to how they were evaluated.
Fire Protection Guide on Hazardous Materials, National Fire Protection Association	No indication is provided on the sources of data or whether they have been 'peer reviewed'. Appendix C of the 12th Edition discusses the preparation of a revised form of the 'Hazardous Chemical Data Sheets' (NFPA 49) contained in this handbook and states that the primary source of information will be material safety data sheets. These are not generally regarded as authoritative sources of data for physico-chemical properties. [References for values are not provided]
Verschueren, K. Handbook on Environmental Data on Organic Chemicals.	A useful discussion is provided of the physico-chemical properties that are covered in Verchueren and how they can potentially be used in assessing environmental behaviour but there is no description of sources used to compile the reported data or how they were evaluated. Ranges rather than single values are sometimes presented for parameters such as water solubility and Log Kow. [References are not given for phys-chem values but they are provided for entries of biological effect levels, bioaccumulation and degradation rates]

Dust Explosions in the Process Industries (by R. Eckhoff)	No physico-chemical data relevant to the SIDS dataset are presented in this reference source other than experimental values for median particle diameter and particle size distribution of various dust types and classifications of flammability (these are non-SIDS endpoints).

3.1.8 Acceptance and use of studies from Industrial Bio-Test laboratories

Background

37. Industrial Bio-Test laboratories (IBT) was one of the largest independent testing facilities in the United States conducting a third of all toxicological testing in the United States before a routine inspection by FDA in 1976 uncovered numerous discrepancies between raw data and study reports, and gross deficiencies in study conduct. The problems were mainly associated with the sections conducting "non-acute" studies[9]. These shortcomings prompted the US FDA to initiate the regulation of laboratory testing, which ultimately led to the development of Good Laboratory Practice which was introduced in 1979. IBT was closed down in 1978.

38. In response to the concerns about the reliability of studies conducted by IBT, the US EPA introduced a legal requirement for study sponsors to audit the raw data and validate IBT studies submitted as part of pesticide registrations, particularly those considered to be pivotal to the regulatory decision making process. Spot-checking of the industry audits revealed some areas of concern leading the US EPA, in collaboration with the Canadian Health and Welfare Department, to set up a post-hoc audit program to formally check the validity of IBT studies. During this audit program, studies were reviewed to determine whether laboratory notes supported the information in the final report and to determine whether they met certain quality requirements (US-EPA, 1983). There is currently no information available as to whether similar concerns apply to environmental toxicity studies conducted by IBT. According to US EPA there is no information or documentation that the environmental toxicity studies were conducted at IBT. It is likely that IBT subcontracted these types of studies to the other facilities and submitted the final reports under its name.

39. Non-acute studies were identified as the main priority because the major discrepancies uncovered were in sections conducting chronic and multi-generation studies. Of the 867 non-acute studies reviewed under the audit programme, 618 were found to be invalid. Significant discrepancies and deficiencies were also noted in the acute toxicity studies; however, all focus was then on the repeated-dose, long-term studies that were mainly used for regulatory purposes. Problems were uncovered in studies conducted during the 1960's and until 1978. Thus studies collected during this period should be considered as problem studies.

40. The issue of whether results from the IBT studies can be used for regulatory purposes has been raised in a number of fora. There has been a somewhat inconsistent approach to the use of the IBT studies, from outright rejection to normal evaluation and use as with any other study. Below is a proposed structured approach to making the most appropriate use of IBT studies, taking into account the various

[9] Study types identified as potential problems:
- Sub-acute
- Sub-chronic
- Carcinogenicity
- Reproductive toxicity (including teratogenicity)
- Genotoxicity
- Neurotoxicity

factors detailed above. The general principles outlined could also be applied to studies from other test houses which are considered to be suspect.

Proposed approach

41. For studies conducted during the suspect period the assumption should be that they are potentially invalid and the findings unreliable. The exception to this is where a study has been formally audited by the regulatory authority and the audit did not uncover any problems, in which case it should be safe to consider the study as of sufficient reliability to be used. If the audit reveals significant problems which impact on the reliability of the findings then the study should be rejected.

42. There may be other factors which provide sufficient confidence to allow the data to be used. These should be considered on a case by case basis. It is also recommended that the issue is not just whether to use or reject the results from an IBT study, as it is considered that the data from an IBT study could be used in different ways depending on the level of confidence attached to it. For instance, data in which there is relatively high confidence could be used as a key study, supporting for example the derivation of a NOAEL or other limit, whereas if there is less confidence in the data it may still be used but down-graded to just supporting or weak evidence (as is often the case for old studies conducted using non-standard protocols). Of course, whenever an IBT study is used the problems and issues raised and a judgement on the reliability of the study (using a reliability score as well as a reliability rationale) should be clearly articulated in the assessment.

43. For example, a study audited only by the study sponsor and not by post-hoc programme might be considered less than totally reliable (given the concerns expressed by EPA on the industry audits which led to the initiation of the post-hoc audit programme) and therefore would only be used as supporting evidence.

44. Another important consideration is the consistency of the findings from the IBT study with findings from other studies that were conducted at reputable test houses at a later date to the IBT study (to rule out the possibility of data being manipulated by IBT to be consistent with existing data). Clearly if the findings are consistent (e.g. the same pathological findings, same target organ, similar dose-response relationship etc) then this would increase confidence in the IBT data, especially if the study has also been adequately audited. Expert judgement is required on a case by case basis to judge how those data should be used, but they may potentially be very useful, reproducing findings in other studies (and hence increasing confidence in the characterisation of that toxic effect of the chemical), or to consolidate a complete picture of the toxicological profile of a chemical, for instance by giving dose-response information at doses not covered by other studies.

45. In cases where there are no other studies available with which to compare, it is unlikely that an IBT study which has not been audited/ validated could be considered to provide anything more than weak evidence. Depending on the programme this situation may lead to a conclusion that there are data requirements. Where there is no independent audit/validation and the IBT study findings are inconsistent with other data then the study should be rejected.

46 In the absence of any information on the reliability of environmental studies signed by IBT, a similar strategy to that described above for the use of such studies is proposed.

Summary

47. In brief the proposed approach (for studies conducted during the suspect period) is:

- When the study has been audited in the EPA / FDA post-hoc programme

    - Use the study as normal if no problems have been highlighted
    - If minor issues that do not invalidate the data have been highlighted then use the study with care as supporting data
    - If the audit reveals significant problems which impact on the reliability of the findings then the study should be rejected

- When the study has been audited by Industry
    - Use the study but use expert judgement to consider the reliability of the findings, for instance by comparing with findings from other studies conducted at a later date in reputable testing facilities
    - If the audit reveals significant problems which impact on the reliability of the findings then the study should be rejected

- When the study has not been audited
    - If the findings are consistent with a study conducted at a later date the study may be used but should be considered as weak evidence
    - If the findings are inconsistent with other studies or there are no other data with which to compare, reject the study

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