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Critical selection of toxicological data on chemicals. The example of the International Register of Potentially Toxic Chemicals data bank

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Summary. - Although chemicals provide important benefits, they can also represent hazards to human health or the environment. However, due to number of chemicals involved, clearly no country can deal alone with the evaluation of existing scientific, technical and legal information on chemicals. This implies a need for countries to work together to assess the risk posed by chemicals and to share the results in a compatible and understandable way. In 1973 the governing council of United Nations Environment Programme (UNEP) decided to proceed with the creation of the International Register of Potentially Toxic Chemicals (IRPTC). The core activity of IRPTC is the collection of information on chemicals into a computerized data bank and the dissemination of these data in the form of chemical data profiles. The data profiles focus on selected chemicals with a potential to affect human health and the environment, excluding chemicals whose sole use is as a pharmaceutical or which are radioactive substances. The data collection and selection activities of IRPTC are driven by two key issues: data quality and data quantity. The objective of IRPTC in this respect is to provide decision-makers and other users with the most pertinent data available to substantiate their assessment of hazard. Providing reliable and detailed data in manageable amounts was the strategy chosen to achieve this objective. To ensure that the information included in the register is consistent with these ideas, IRPTC has developed detailed instructions to define as accurately as possible the data that should be entered into the register.

Key words: databases, registries, quality assessment, toxicology, hazardous substances.

Riassunto *(Selezione critica di dati tossicologici sulle sostanze chimiche. L'esempio della banca dati dell'International Register of Potentially Toxic Chemicals).* - Nonostante gli indubbi benefici, le sostanze chimiche comportano dei rischi per l'uomo e l'ambiente. Il loro enorme numero, inoltre, impedisce che un singolo paese possa completare da solo lo studio e la regolamentazione di tutte le sostanze chimiche esistenti. Ne deriva la necessità della cooperazione internazionale nella valutazione del rischio chimico e nella condivisione delle informazioni. Nel 1973, pertanto, il comitato esecutivo dell'United Nations Environment Programme (UNEP) decise la creazione dell'International Register of Potentially Toxic Chemicals (IRPTC). L'attività precipua dell'IRPTC è l'immissione di dati sulle sostanze chimiche in un database computerizzato e la loro divulgazione sotto forma di "data profiles". I data profiles riguardano quelle sostanze chimiche con un potenziale impatto sulla salute e l'ambiente, con l'esclusione dei farmaci e delle sostanze radioattive. Due sono i criteri-guida dell'IRPTC nella raccolta e nella selezione dei dati: la qualità e la quantità dei dati. In proposito, l'obiettivo dell'IRPTC è quello di fornire agli utenti, in particolar modo amministratori e governi, i dati esistenti più utili alla valutazione del rischio. La strategia scelta per il perseguimento di questo obiettivo è quindi quella di fornire dati attendibili, dettagliati ed utilizzabili. A questo scopo l'IRPTC ha sviluppato delle istruzioni dettagliate per identificare il più accuratamente possibile i dati che entrano a far parte del registro.

Parole chiave: banche dati, registri, valutazione di qualità, tossicologia, sostanze chimiche pericolose.

Introduction

The number and the variety of chemicals to which man and his environment are exposed are increasing every year. Though chemicals provide important benefits, they can also represent hazards to human health or the environment. Of more than 11 million known chemicals, around 80,000 are in commercial use. The appropriate management of these chemicals has thus become one of the major problems of present times.

This challenge can only be met if informed decisions are taken after having evaluated whether the benefits of the chemicals to be used in a country outweigh the real or potential risks. Such decisions must be based on, among other factors, the evaluation of existing scientific, technical and legal information on chemicals. However, due to the number of chemicals involved, clearly no single country can deal with this issue. This implies a need for countries to work together to assess the risk posed by chemicals and to share the results in a compatible and understandable

way. The use of a compatible international mechanism for the exchange of data and results of evaluations would clearly facilitate international cooperation.

The United Nations recognized in 1972 during the Conference on the Human Environment (UNCHE) that to properly address the challenge expressed above would have been necessary to involve the establishment of an international register for chemicals and a global network for the exchange of information to be managed through the register. The governing council of United Nations Environment Programme (UNEP), itself established in 1973 on the basis of a recommendation from UNCHE, decided to proceed with the creation of the International Register of Potentially Toxic Chemicals (IRPTC). Further to the work of a group of experts during 1975 who drew up guidelines for the establishment and operation of IRPTC, the governing council agreed on a number of objectives to be achieved by IRPTC.

Updated in 1989, these objectives are as follows:

1) to facilitate access to existing data on the production, distribution, release and disposal of chemicals and their effects on man and the environment, and thereby contribute to a more efficient use of national and international resources available for the evaluation of the effects of the chemicals and their control;

2) on the basis of information in the register, to identify important gaps in existing knowledge on the effects of chemicals and call attention to the need for research to fill those gaps;

3) to identify, or help identify, potential hazards for chemicals and wastes and to improve the awareness of such hazards;

4) to provide information about national, regional and global policies, regulatory measures and standards and recommendations for the control of potentially toxic chemicals;

5) to facilitate the implementation of policies necessary for the exchange of information on chemicals in international trade.

The IRPTC data bank

The core activity of IRPTC to achieve the objectives listed above is the collection of information on chemicals into a computerized data bank and the dissemination of these data in the form of chemical data profiles. The data profiles are on selected chemicals with a potential to affect human health and the environment, excluding chemicals whose sole use is as pharmaceuticals or which are radioactive substances.

One data profile is an integrated data set covering a range of subject areas related to hazard identification and risk assessment of chemicals. It contains the maximum of relevant information in a minimum of space. To achieve this, IRPTC has adopted a computer-assisted standardized presentation of data that is scientifically sound and comprehensive, but relies considerably on the use of abbreviations.

The data profiles, containing extracted factual, numeric and non-numeric data, are organized in seventeen data files that are further subdivided into subfiles where necessary. Each data file or subfile contains data records that consist of a set of data generally derived from one scientific article or study and accompanied by a reference. Data are presented in semi-tabular form using an abbreviated format. Every item of data has been given a defined space called data field. In each data record a space is reserved to accommodate comments on specific aspects of the study.

The data files dealing with toxicological aspects, are the data file 10, mammalian toxicity, and the data file 11, special toxicity studies. In this latter data file the following subfiles are contained: 11.1. biochemical interactions; 11.2. carcinogenicity. 11.3. mutagenicity; 11.4. neurotoxicity; 11.5. behaviour; 11.6. sensitization; 11.7. interacting agents; 11.8. primary irritation; 11.9. immunotoxicity; 11.10. reproduction; 11.11. teratogenicity.

The whole list of data files considered in the IRPTC data bank is as follow:

1. identifiers, properties and classification; 2. production/trade; 3. production process; 4. use; 5. pathways into the environment; 6. concentrations; 7. environmental fate tests; 8. environmental fate; 9. chemobiokinetics; 10. mammalian toxicity; 11. special toxicity studies; 12. effects on organisms in the environment; 13. sampling/preparation/analysis; 14. spills; 15. treatment of poisoning; 16. waste management; 17. recommendations/legal mechanisms.

From data collection to the production of data profiles

The data collection and selection activities of IRPTC are driven by two key issues: data quality and data quantity. The objective of IRPTC in this respect is to provide decision-makers and other users with the most pertinent data available to substantiate their assessment of hazard. Providing reliable and detailed data in manageable amounts was the strategy chosen to achieve this objective. To ensure that the information included in the register is consistent with these ideas, IRPTC has developed detailed instructions in order to define as accurately as possible the data that should be entered into the register.

The production of a data profile is the final result obtained by carrying out the actions listed in Fig. 1.

Literature selection

The first step for the implementation of a data profile is the selection of sources from scientific literature. To meet concerns for data quality and quantity, IRPTC uses data sources in the following order of priority:

- international monographs and criteria documents containing evaluated information, e.g. those of the International Agency for Research on Cancer (IARC), the International Programme on Chemical Safety (IPCS), and the Food and Agriculture Organization (FAO);

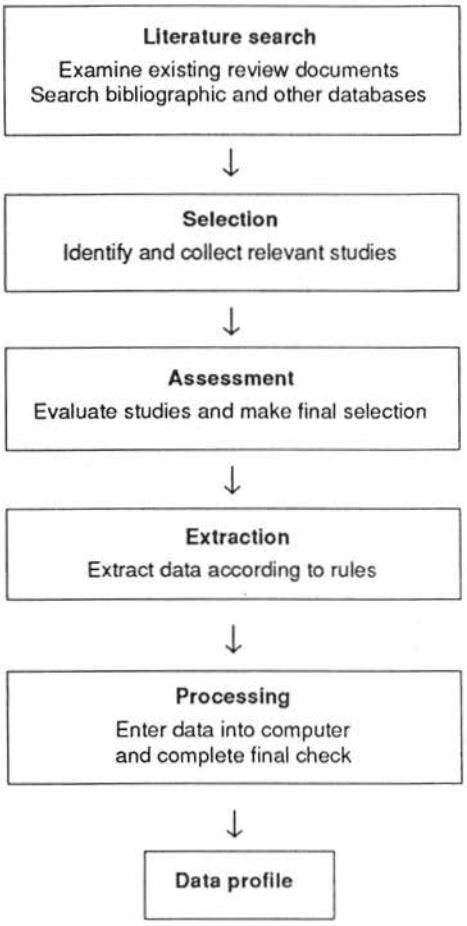

Fig. 1. - How to produce a data profile.

- national monographs, reviews and criteria documents containing evaluated information, e.g. those prepared by expert panels convened by national agencies, such as *inter alia* the US National Institute for Occupational Safety and Health (NIOSH, producing the NIOSH criteria documents), the US Environmental Protection Agency (EPA), the National Research Council of Canada (NRCC) and the UK Health and Safety Executive (HSE);

- national monographs, reviews and other documents containing non-evaluated information, e.g. individual articles from symposia organized by national agencies; publications prepared by non-governmental organizations, such as the International Commission for Protection against Environmental Mutagens and Carcinogens (ICPEMC) and the American Conference of Governmental Industrial Hygienists (ACGIH); reviews published by individual authors, although these reviews must themselves be evaluated for quality of literature coverage and analytical expertise;

- articles in scientific journals, reports made available by industry (primary literature).

The first two categories constitute the evaluated "secondary literature".

By using the secondary evaluated documents such as reference sources, IRPTC includes studies that have been validated by groups of experts. To be complete and ensure that the data are correct, IRPTC normally extracts the data from the original articles.

When evaluated documents are not available or certain files cannot be covered, IRPTC uses other secondary documents as reference sources and also searches in the available bibliographic data bases. The latter are also consulted to update the data profile with data published after the period covered by the secondary documents.

An important aspect in this context should be stressed: when many papers have been published on essentially the same subject, IRPTC does not attempt to be fully comprehensive. A basic concept has always been to draw the reader's attention to relevant aspects of chemical toxicity without necessarily covering all the test species that may have been considered or all the experimental conditions that may have been systematically applied. Although comprehensiveness may eventually give interesting scientific insight, it does not necessarily shed new light on the hazardous properties of a chemical substance. Therefore, IRPTC is a factual database that is comprehensive regarding the data elements included (i.e. the files and subfiles as well as the data fields contained in each record of a file or subfile), but not necessarily exhaustive in terms of literature coverage.

Reliability of data

When selected characteristics have been listed and pertinent sources of information identified, the reliability of data has to be ascertained before they are entered into the database. With the advancemement of research, findings frequently become controversial and may reverse earlier conclusions or introduce new concepts. Moreover, different interpretations of experimental observations are also possible. Data evaluation, therefore, is essential for a valid understanding of the chemical, physical, biological and toxicological characteristics of a substance. Experts' deliberations and judgements are indispensable for hazard assessment and to define precise values for concepts such as "acceptable daily intakes", "maximum permissible concentrations", "no effect levels", etc. Such evaluation results are only available for a limited number of chemicals and for specific data files or attributes. Admittedly, duplication of effort is not uncommon among the agencies performing this task. The effective use of the IRPTC may reduce in the future such duplication thus leading to a more rationale use of resources for the evaluation of a greater number of chemicals.

For many attributes, evaluation by qualified agencies has not been performed. This is especially true for the effects of chemicals on species other than man. Similarly, evaluations in the treatment of chemical intoxication produced by long- and short-term exposure of man to chemicals have not been adequately performed. Data evaluation by panels of experts should more timely address new problems, as they are recognized either by data that are suggestive of potential injury or by the absence of such data.

In any case, the reader requirements and own criteria are, and will remain, the decisive issues in the field of data reliability. Citations from the reports of the different institutions which review and evaluate data are, therefore, provided to the user so that he can select from available secondary literature those documents in which he/she is more confident. An information system on chemicals should at best indicate the type (evaluated or non-evaluated) of information that it contains. The IRPTC system of citing references uses a special mark to call the reader's attention to the fact that evaluated information is quoted.

Secondary documents do not exist, however, for the great majority of chemical substances. The absence of citations in the data records for such reviews and/or evaluations for a particular substance indicates that the data presented have not been evaluated by a panel of experts. Therefore, the level of reliability is not ascertained. In such a case, experts acceptable to the user can be employed for hazard evaluation or the appropriate national or international institutions can be petitioned to undertaken the task.

IRPTC instructions for data selection and extraction

Instructions have been developed by IRPTC with the purpose of facilitating data selection and presentation. During their preparation, wide use has been made of existing national and international documents giving guidance to methodology for testing chemicals [1-8]. The IRPTC instructions define, as accurately as possible, what data should be entered into the register. They have been designed to be sufficiently structured so as to provide precise guidelines to extract the pertinent information from scientific literature. Evidently, this information must be comprehensive enough to permit the "best-informed" judgement of decision makers who have to assess hazards posed by chemicals. On the other hands, as data extraction increases and experience is gained with preparation of data profiles, new situations can arise that will require attention. As a result, the instructions should be routinely monitored and revised by the IRPTC with the assistance of expert consultants to ensure that they reflect current knowledge in the various subject areas.

There are several advantages with this approach. With a well-established format and standardized instructions for data selection, data can be processed in widely separated geographical areas, thereby making it possible for network partners to produce data profiles. The instructions provide a model and the data prepared using this model can later be monitored by the IRPTC to assure that it is consistent with the design of the register. This will make it possible to evaluate the reliability of the data and make the best use of it for the user's own particular needs. Further, an abbreviated and standardized format enables the effective use of the register for updating, i.e. for monitoring current publications for new information.

The process of defining the attributes is dynamic and reflects the experience acquired during a review of the literature for data extraction. When one first attempts to extract data from the literature, multiple decisions concerning the selection of data must be faced. A possible approach would be to include all data that have been published on the chemicals under study. In this case the factual data bank would very quickly become unwieldy and its development very costly. Moreover, no control of the quality of data could be implemented.

Another possibility would be to use exclusively secondary evaluated documents. However, this approach would leave too many incomplete data files, since only a relatively small number of chemicals have been reviewed and evaluated. The secondary documents provide a useful mechanism for dealing with the abundant primary literature available for some chemicals. As outlined above, they only contain data that, according to expert opinion, qualify for inclusion into a secondary evaluated publication.

Although the available secondary documents are used by the IRPTC to facilitate literature selection, the data themselves are extracted from the primary literature where the information is more comprehensive.

For the majority of chemicals in the register, primary literature will often be the only source of published information available. In fact, for a large number of chemicals, data selection will not be an issue as there are very little data available.

Primary literature is also essential for updating the register. Updating should be an ongoing process using both primary literature and newly published secondary documents.

Practical problems related to the selection of data have been identified and carefully studied by IRPTC. Though open to improvement, workable solutions have been developed.

A general presentation of these "selection rules" as they apply to the data files reporting on toxicity data is outlined below. Detailed guidelines more specific to these and other data files of the register are described in the publication *Instructions for the selection and*

presentation of data for the International Register of Potentially Toxic Chemicals [9]. This manual published in 1979 has been considerably revised and expanded since then.

Selection rules for toxicity data

As said before, when many selected articles published on essentially the same subject are available, this may result in very large data profiles. IRPTC does not attempt to be fully comprehensive. A pragmatic attitude adopted by IRPTC in such cases is based on the fact that a large number of studies related to a particular compound point to a compound giving rise to concern. Therefore, secondary literature most likely exists. This probably eliminates unreliable and less reliable studies as well as hard-to-interpret observations.

Major problems may arise when no "secondary evaluated documents" are available. In this case:

1) one toxic effect is described in one species in many papers, but most of them report on changes in results when the experimental conditions or parameters are modified;

2) correlations of various types are reported in many documents;

3) one toxic effect is described in many species.

An always true and applicable priority ranking of selection rules is not easy to develop and often more importance will have to be given to one point rather than to another on a case-by-case basis.

The main elements of the strategy followed by IRPTC in extracting toxicology data from scientific documents are outlined hereafter.

1) Toxic effects are reported. All of them.

2) Data on human beings are always reported.

3) The lowest dose (or concentration) at which an effect is observed is chosen.

4) The no effect level is always reported.

5) Studies where the results have been statistically analyzed following currently accepted methods are entered by preference. This implies that a laboratory study with a control group is considered as more indicative for the register as compared with a hard-to-interpret so-called field study based on a few case observations of the same effect.

6) Epidemiological studies with a control group and statistical analysis of the results are always entered. When there are no such studies, case reports can be entered provided that the correlation between the chemical and the effect is clearly established.

7) Particular attention is given to changes in experimental conditions that modify the experimental observations and give various correlations, thus resulting in a large number of papers:

7.1) If the results are significantly changed, as stated by the authors, the smallest modification of experimental conditions responsible for this is considered as a piece of information that should be entered.

7.2) Changes due to age of population, variations of fat or protein intake and other essential nutrients contained in feeding stuffs, are always reported with the same limitations as in 7.1 with respect to the significance of the results.

7.3) Changes observed under other modified experimental conditions (temperature, pH, relative humidity) are only included if the latter are in a reasonable range not too remote from normal (ecological) conditions. This does not exclude reporting of data in other data files such as on "spills" (file 14.01) and "poisoning" (file 15.01).

8) As regards the same toxic effect described in several species:

i) in addition to human data, toxicological data on a rodent and a non-rodent species are reported whenever possible;

ii) some fields of special interest to human beings can be useful criteria of choice, as regards, e.g. animal species used for human consumption or species of economic importance.

Rules for selection of toxicological data to be included in the IRPTC data bank

The data files "mammalian toxicity" (data file 10) and "special toxicity studies" (data file 11, data subfiles 11.1 to 11.11) concern the acute, subchronic and chronic toxicity studies in mammals.

A record in this section includes in general the following sections: a) test description; b) test results; c) general comments; d) evaluation and appraisal; d) references.

A list of the data fields contained in each section of the data file on toxicity in mammals is reported in Table 2. Selection criteria have been developed for each data field and will be described in detail in the following.

Test description section

Study type data field. - In case of similar observations, results from laboratory or epidemiological studies are recorded in preference to case reports or spill studies or less controlled "outdoor" studies on domestic animals. Studies that have been evaluated as inadequate in secondary documents are not entered in the data base. If a study is not completely rejected, but commented upon as being somehow inadequate, pertinent comments must be entered in the sections "general comments".

Organism data field. - Data on both mammalian and non-mammalian species are included in the special toxicity studies, whereas the mammalian species are the only species considered in the mammalian toxicity data file. When several studies show the same effect, the organisms and species suggested in international and

Table 1. - General mammalian toxicity and special toxicity studies: data fields

Test description

- study type
- organism
- route
- sex
- lifestage
- number of organisms exposed
- number of organisms in the control group
- species/strain//system description
- exposure dose/concentration
- exposure period
- exposure type
- exposure frequency
- exposure comment
- purity grade and/or percentage
- impurities
- vehicle/solvent
- description of the test substance/particle size
- isotope/labelled compound
- test conditions/method

Test results

- organ/system/tissue affected
- effect
- sex affected
- reversibility/irreversibility of the effect
- time of onset of the effect
- number of exposed affected
- number of controls affected
- effect comment
- general comments
- evaluations and appraisals

Reference

- status of the secondary document (e.g., if evaluated)
- secondary-reference
- status of primary document (e.g., if unpublished)
- primary reference

national test guidelines are preferably selected. Human data are included, even if the information available is not complete, e.g. if no dose/concentration is available. When similar results from many experimental studies are available, at least the three giving the most complete information are selected.

Route of exposure data field. - The most common routes of human exposure are inhalation, oral and dermal. Data on these routes are selected when many studies show the same effects. Data on other routes (intramuscular injection, intraperitoneal injection, etc.) may be entered depending on the use and physical properties of the substance and if no other data are available for a particular effect. *In vitro* studies will be most frequently recorded in the subfiles "biochemical interaction" and "mutagenicity"

Sex data field. - In general, studies including both sexes are preferred.

Number of exposed animal data field. - When several studies show the same effect, the results are preferably selected from those complying with international and national test guidelines.

Number of control animal data field. - International and national test guidelines point out that the number of controls should be at least as high as the number exposed per dose/concentration. Information on other control groups, i.e. positive or historical controls, can be entered in the field general comments.

Exposure dose/concentration data field. - If in a particular study more than one dose is reported to cause the same effect(s) the minimum dose required to cause the effect is selected and entered, together with the highest dose/concentration causing no effect.

Exposure period data field. - International and national test guidelines point out that an exposure frequency of 7 days per week is preferred, but also 5 days per week is acceptable. For inhalation studies, animals are usually exposed 6 hours per day (industrial studies) although, for environmental studies, exposure should preferably be 22-24 hours per day. Studies that conform to these test guidelines are preferably selected for the register. Variable time/period/frequency pattern of exposure must be clearly described in the exposure comment field. When reported to be of relevance to the observed effects, supplementary information on: a) type and/or condition of employment; b) illness and treatment in case report; c) emergency measures and treatment can be reported.

Test results section

Studies reporting statistical analysis of results are preferred.

The organ, systems or tissues reported to be affected are entered together with the actual effect, its reversibility/ irreversibility, the sex and number of organisms affected (in both exposed and control groups) and the time of onset of the effect. Also effects not related to a specific organ system or tissue - such as death, body weight change or subjective symptoms - are entered in this section.

When no effects are found at a specific dose/ concentration, a NEL figure will only be entered when evaluated and reported as such by an international or national group of experts, e.g. as in the WHO/FAO evaluations of pesticide residues in food. When it is not evaluated, the abbreviation NEF (no effect reported) is used. In either case data on organ/tissue/system affected are entered as effect comments. In this field details are entered concerning the effects observed and statistical analyses of the experimental observation (type of test used and probability levels).

General comments section

This is a free text section that should be used to highlight circumstances that may have significantly influenced the results of the study. Whenever possible, this information is entered as reported.

Additional information, considered to be important by the author(s), can also be included: a) compliance with specific guidelines; b) conclusion drawn from test results; c) factors reported to cause uncertainties in the interpretation of results; d) controversial evaluations concerning the validity of the study, i.e. its rejection or acceptance by different international or national group of experts.

Evaluation and appraisal section

Evaluation and appraisal with respect to the effects and actions of the substance made by international or national groups of experts are included as a quotation in free text, e.g listing of main acute effects and cause of death, chronic effects and evaluations made concerning the chemical's carcinogenic, neurotoxic or teratogen potential, etc. The reasons supporting the explanation of the conclusion are also quoted. When there is no evaluation or appraisal prepared by international or national groups, conclusion or summaries made by the authors can be entered, but an internal discussion in IRPTC, and in some case external scientific expertise, are requested.

Reference section

The final part of a data record is the reference section that includes: a) status of the secondary documents; b) secondary reference; c) status of primary documents; d) primary reference.

All references are given a unique six-letter code (CODEN) which identifies the publication. When available, CODENs prepared by the US Chemical Abstract Service are used. When no official CODENs are available, a pseudo-CODEN is prepared by the IRPTC staff. The reference field gives information on the status of the document. For example, the reference for evaluated secondary documents begins with an exclamation mark; a sign '#' indicates an unpublished document submitted to IRPTC for data extraction.

The full title of the document, the volume number, the page number(s), and the year of publications follows the CODEN.

Conclusions

IRPTC was conceived to operate a network that should bring together all involved parties in the evaluation of chemicals for their safe use. This cooperation will help the national and international communities in a proper use of chemicals

To be effective IRPTC strives for selecting, collecting and integrating scientifically sound and reliable data on chemicals.

Informed decisions, based on scientific knowledge will guarantee progress and development, in particular in developing countries, without endangering human health or the environment.

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