The ISS National Inventory of Chemical Substances (INSC)

Roberto Binetti, Francesca Marina Costamagna, Federica Ceccarelli, Antonella D'Angiolini, Alessandra Fabri, Giovanni Riva, Susanna Satalia and Ida Marcello
Dipartimento di Ambiente e Connessa Prevenzione Primaria, Istituto Superiore di Sanità, Rome, Italy

Summary. The INSC *(Inventario Nazionale delle Sostanze Chimiche)*, a factual data bank, produced by Istituto Superiore di Sanità (ISS), consists of an electronic tool on chemical information developed for routinary and emergency purposes. Historical background, current status and future perspectives of INSC are discussed. The structure and the feature of INSC are briefly examined. Aspects of information retrieval and the criteria for inclusion of data and priority selection are also considered.

Key words: factual data bank, chemical database, hazardous substances, toxicological information.

Riassunto *(L'Inventario Nazionale delle Sostanze Chimiche)*. Viene presentato l'Inventario Nazionale delle Sostanze Chimiche (INSC), banca dati fattuale sulle sostanze chimiche prodotta dall'Istituto Superiore di Sanità. L'INSC è stato sviluppato sia per emergenze che per ogni situazione che coinvolga sostanze chimiche. Vengono brevemente illustrate la struttura e le caratteristiche dell'INSC e presentati i criteri per la scelta dei dati da inserire e per la selezione delle priorità. Vengono inoltre esaminate le fonti di informazione utilizzate.

Parole chiave: banca dati fattuale, sostanze chimiche, sostanze pericolose, informazione tossicologica.

INTRODUCTION

The Seveso accident, the most serious event of environmental release of a highly dangerous chemical (2,3,7,8-TCDD), which took place in Italy in July 1976, stimulated the definition at European Union level of many important prevention and emergency response strategies. Among them, the well known EU "Seveso Directive" [1]. In that period, the Istituto Superiore di Sanità (ISS), under the leadership of its Director, Francesco Pocchiari, significantly increased its activity in the chemical hazard studies and the related advises and information production, collection and diffusion, on request by the Ministry of Health and by the regional and local public health institutions [2]. A new structure was organized and a dedicated informatic system storing hazardous chemical data and evaluations was set up, at care of Angelo Sampaolo, who directly pointed out the essential need of updated and relevant data during his major role in the very first emergency response to the Seveso accident [3].

In the framework of a structural revision of the National Health Services the Seveso event and the indications deriving from Directive 79/831/EEC concerning the new EU policy introducing a notification procedure for *new chemicals* [4], stimulated the Italian Ministry of Health to insert in the Law n. 833 of 23 December 1978 a new article (art. 9), which appointed the ISS as the institution responsible for organizing and regularly updating the National Inventory of Chemical Substances (*Inventario Nazionale delle Sostanze Chimiche,* INSC) [5] .

The role of the ISS in scientific advising toward the national health institutions implied the predisposition of computerized toxicological profiles characterized by a standard, flexible structure, aimed at responding to specific questions posed by the system users. The dialogue between the INSC experts and the end user institutions, allowing the optimization of the requested information setting up and of the problem solving, has been and is a peculiar characteristics of this system, allowed to appropriately respond to objectively existing needs. These characteristics involving a bidirectional contact with the information user is still important and a "friendly" approach in data providing seems still valid for improving and extending, whenever necessary, the requested information. Moreover, this solution also prevents a misunderstanding of the role of INSC, which is to provide information and not to present an official opinion of the ISS (except for the cases where a formal ISS opinion is expressly reported as such). However, public health institutions may be helped to receive an official ISS opinion through the INSC staff. It is worthwhile noticing that, throughout the ages, the information requested, even if not online, is made available in a very short time (this solution has been adopted for taking into account requests of specific information, whenever necessary).

Address for correspondence: Roberto Binetti, Dipartimento di Ambiente e Connessa Prevenzione Primaria, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: roberto.binetti@iss.it.

The INSC started its activity in the year 1981, practically being the only data bank in Italian language available at national level on chemical hazard. The information users were and still are national ministries, national central, regional and local public health institutions, universities, and other public organizations dealing with chemical risks for the general and occupational populations and for the environment. Moreover, the INSC has been and is regularly updated taking into account the progressive evolution of EU and national regulations and laws in the field of chemical risk.

The INSC is still in Italian for facilitating the consultation by national users, to whom it is mainly dedicated. The main users have been the personnel of local (ASL) and regional agencies for health and regional environment protection (ARPA), as well as the Ministries of Health, of the Environment, of Work, of Interiors, the Civil Protection, and various scientific committees. At international level, the INSC has also provided, in the 80s, an important contribution to a WHO committee on drinking water quality and has provided more than 500 monographic datasheets on pesticides for EU hazard classification purposes in the context of Directive 67/548/EEC [6].

It is worthwhile mentioning that bidirectional relation among the INSC experts and the Public Health experts has clearly underlined the need of making available quantitative risk parameters, essential for risk practical management in the various national contexts. The INSC was therefore extended including a large amount of these data, so that both qualitative and quantitative risk estimations and criteria are made available. The INSC has been and is a *trait d'union* between the information, selection and presentation activity and the request of ISS official evaluations and opinions. The very high number of information requests received so far by the INSC can clearly demonstrate the success of this initiative and the high level of the personnel that have heavily and efficiently worked for providing a suitable support for risk prevention.

THE STRUCTURE OF THE INSC

The INSC is a factual data bank, of easy consultation, with information organized in the form of monographs, written and structured as book chapters and with standard sections and subsections, each of them independently addressable.

At the present time, fourteen categories of data and more than 200 subcategories are available, covering the broad subject areas presented in *Table 1* and synthetically described below.

1. Substance identity. The first step of the information gathering process is the identification of the chemical of interest. In fact, the same chemical may have many synonyms, thus complicating the search. The INSC structure allows a rapid and exact retrieval of the searched substances on the basis of nomenclature and identification codes. The section includes:

- ***EC name:*** generally the name adopted in the Annex I to Directive 67/548/EEC or in the EINECS for substances not officially classified by EU;
- ***IUPAC name:*** the IUPAC (International Union of Pure and Applied Chemistry) nomenclature is a systematic way of naming chemical substances, both organic and inorganic. In IUPAC nomenclature, prefixes, suffixes and infixes are used to describe the type and position of functional groups in the substance. In the INSC IUPAC name is obtained from secondary sources;
- ***synonyms:*** other international chemical name(s) (*e.g.,* ISO name), usual name, generic name, proprietary or trade names, generic names and abbreviations;
- ***CAS name*** (if available): is the name given by the Chemical Abstract Service (CAS), a division of the American Chemical Society (ACS), to every chemical which enters the registry database and it is different from the IUPAC name. In the INSC the CAS name is in English language and is obtained directly from the Chemical Abstract Service Registry file (www.cas.org);
- ***Annex I name:*** is the name used for the substance in Annex I of Directive 67/548/EEC on classifica-

Table 1 | *The fourteen categories of data*

1	*Substance identification* (nomenclature, identification codes, formulas)
2	*Use pattern, production, treatment methods and precautions* (precautionary criteria for the handling, transport, storage, incompatibilities and dangerous reactions)
3	*Physico-chemical properties*
4	*Toxicological data on mammals* (acute, sub-acute, sub-chronic, chronic toxicity, specific effect such as carcinogenicity, mutagenicity, reproduction and developmental toxicity, neurotoxicity, metabolism)
5	*Ecotoxicological data* (acute and long term effects on aquatic and terrestrial organisms; bioaccumulation)
6	*Environmental studies* (environmental fate; chemical reactivity and degradation; photochemical transformation; biodegradation; contamination studies in different media)
7	*Studies on humans* following acute and repeated prolonged exposure both occupational and non-occupational; metabolism
8	*Emergency and/or inactivation measures* (in the case of accidental spillage or injury to persons)
9	*Complementary data for particular applications and uses*
10	*Threshold values* (Threshold values, guidelines and other parameters for occupational and general population protection)
11	*Hazard classifications*
12	*Available national and international classifications, evaluations and assessments* (IARC; CCTN ; NTP; RoC; USEPA; other international evaluation such as IPCS, NIOSH; ECETOC; JECFA FAO/WHO; JMPR FAO/WHO; OECD; BIBRA)
13	*Bibliographic references*
14	*Updating*

tion, packaging and labelling of dangerous substances. Many substances appear in the Annex under different synonyms. It is obtained from the web site of ECB (http://ecb.jrc.it/);
- ***Colour Index Generic Name:*** obtained from *Colour Index*, a commercial database of dyes classified by their Colour Index Generic Name and Colour Index Constitution Number produced by Society of Dyers and Colorists (from Colour Index International, Fourth Edition Online) (www.colour-index.org);
- ***CAS number*** (if available): provides the only reliable key for the chemical substance identification. It is an unique numerical identifier created and assigned by the Chemical Abstract Service (CAS) to a substance when it enters the CAS REGISTRY database. It is internationally recognized and designates only one substance. It has no chemical significance. The use of incorrect CAS number in searches could lead to irrelevant or inappropriate information. For the purpose of the INSC, CAS number is obtained from the CAS REGISTRY file (www.cas.org);
- ***EC number*** (if available): the EC number corresponds to the EINECS number for existing chemicals (listed in European Inventory of Existing Commercial Chemical Substances), or to ELINCS number for new chemicals (listed in European List of Notified Chemical Substances) or NLP number for substances listed in the No-Longer Polymer List. It is the official number of the substance within the European Union and is obtained from the official publications of EINECS, ELINCS and NLP and of the European Chemicals Agency. The EC Number consists of 7 digits of the type XXX-XXX-X. Information on EC number is obtained through the website of the European Chemicals Bureau (http://ecb.jrc.it) in the sub-section "ESIS". Some substances have no EINECS or ELINCS number;
- ***Index number:*** the index number is the identification code given to the substance in Annex I of Directive 67/548/EEC. It is in the form of a digit sequence of the type ABC-RST-VW-Y;
- ***ISS number:*** numeric code assigned by the National Inventory of Chemical Substances of Istituto Superiore di Sanità [7];
- ***CI number:*** the Colour Index constitution number is an internationally recognized code assigned to a particular "colorant." The CI name consists of the category (type of dye or pigment), general hue and serial number assigned, based on its chemical constitution. The CI number is a five-digit reference number assigned in the Colour Index based on the chemical structure of a colorant, regardless of usage class. CI number is obtained from Colour Index on line (www.colour-index.org);
- **molecular and structural formulas** including molecular weight;
- ***possible related substances:*** a subsection provides reference substances, which are structurally similar to the concerned substance. This is the case of isomers, precursors, analogues (*e.g.,* hydrate forms or salts), relevant derivatives (in the case of pesticides, their salts or esters) or metabolites.

2. Use pattern, production and treatment data. The section includes:
- ***use:*** a brief description of substance uses (*e.g.,* solvent, intermediate, pesticides). Detailed uses are reported in section 9;
- ***indication of production volume in the European Union:*** in order to obtain an indication of the importance and the diffusion of interested substances, the INSC reports for each agent included its production volume within the European Community. Indications, obtained through ESIS (European chemical Substances Information System), an IT (Information Technology) system which gives access to information on chemicals on the European Chemicals Bureau (ECB) web site (http://ecb.jrc.it), make reference to HPVC substances (High Production Volume Chemicals) listed in the Annex I to the Regulation 93/793/EEC [9] on the evaluation and control of the risks posed by the Existing Chemicals, which have been imported or produced within the European Community in quantities exceeding 1000 tonnes per year per manufacturer/importer. The current HPVCs list contains 2767 of these chemical substances; or LPVC substance (Low Production Volume Chemicals), produced or imported in quantities between 10 and 999 tonnes per year within the European Community. The current LPVCs list contains 7802 chemical substances. The production volume of agents in EU is checked and reported and it is indicated the lack of data on production volume;
- ***precautionary criteria for the manipulation, transport, storage as well as rules in case of fire and chemical incompatibilities:*** this subsection provides information on safe handling and personal protection, hazardous reactions, incompatibility, possible violent interaction with other compounds, fire hazard, hazard prevention, engineering control dealing with accidents and spillages, safe storage, transportation and, generally, all information or data on the hazard involved in laboratories, industrial workplaces and in the general environment during handling of chemicals. Moreover conditions and materials to avoid as well as hazardous decomposition products (*i.e.,* hazardous materials produced in dangerous amounts upon decomposition) are also reported.

3. Physical-chemical properties: the physical-chemical properties play a pivotal role from a toxicological and ecotoxicological point of view. Simple physical properties are helpful for predicting routes of potential exposure (water solubility, vapour pressure), accumulation in biota (fat solubility, n-octanol/water partition coefficient) and in general, potential environmental fate. The section moreover

includes melting and boiling points, pH, relative density, fat solubility, partition coefficient, vapour density, flammability (flash point, flammable limits), explosive properties (explosive limits), oxidizing properties. These data also provide important parameters commonly used for the assessment of the environmental partitioning and distribution processes and for the environmental fate prediction, for bioaccumulation prediction, for exposure scenarios identifications, other.

4. Toxicological data on mammals: the information in this section include acute, sub-acute, sub-chronic and chronic/long term toxicity data in experimental animals, for ingestion, inhalation and dermal exposure, reporting the basic experimental study data, necessary for a toxicity evaluation (*e.g.*, species, strain, number of animals used for treatment groups, treatment doses, treatment duration, detected effects, dose-response data, statistic evaluations, other). The acute effects together with the relevant doses are reported for each considered agent. Irritation, corrosion, sensitization experimental data are reported. The chronic effects (2 year rodent studies) including the available data on CMR effects (carcinogenicity, mutagenicity and toxicity for reproduction), neurotoxicity are presented. The available data on toxicokinetic and body distribution, bioaccumulation, elimination and other relevant data are also reported.

5. Ecotoxicological data: ecotoxicological data, including the available effects on aquatic species (fish, amphibians, daphnia magna, algae) and terrestrial vegetal and animal species (plants, invertebrates, birds, other), whenever possible accompanied by metabolism data and bioaccumulation potential are reported.

6. Environmental studies: environmental studies, including reactivity, persistence and degradability, transformation, soil absorption and desorption, biodegradation, food chain impact and contamination, soil, water and air levels are reported. The chemical-physical properties above mentioned play an essential role in these processes.

7. Studies on humans: effects on humans, emerging from the available epidemiological studies on occupational and general populations for short term and chronic exposure or for exposures in accidental events are reported. In the field of chronic effects, the available studies on general toxicity, carcinogenicity, reproductive toxicity, neurotoxicity, other relevant effects are summarized.

8. Emergency andlor inactivation measures: the available information on emergency measures and criteria to be adopted in case of accidental environmental release and people exposure are considered, together with available data on environmental rehabilitation (decontamination, neutralization, elimination or destruction).

9. Complementary data for particular applications and uses: the uses of the examined substance in a large number of different specific sectors are presented, *e.g.,* pesticides production and use, food additives and food flavouring and colouring agents, drugs for human and animal use (as such and during their production), cosmetics (as such and during their production), disinfesting and disinfectant agents for personal, domestic and veterinary use, paints, adhesive agents, inks, preparations for domestic use, materials in contact with food, drugs, and biomedical materials, fertilizers, other.

10. Threshold values: the section contains reference values established at national and international level from expert bodies that review and evaluate available data *(Table 2)* such as:

- ***threshold values and other parameters for occupational health protection such as*** EU occupational exposure limits (OEL) and standards as threshold limit values (ACGIH TLVs), OSHA and NIOSH recommendations and limits, conversion factors from ppm to mg/m^3 and vice versa, Immediately dangerous to life or health (IDLH, reference parameter for accident conditions – the highest in air concentration allowing the exposed people for a short time to move away from the affected areas), other occupational limits;
- ***threshold values and other parameters for general population protection such as*** WHO Air Quality Guidelines and Guidelines for Drinking Water Quality; WHO and other institution ADIs (acceptable daily intakes) and TDIs (tolerable daily intakes) for ingestion exposure. US Environmen-

Table 2 | *Expert group evaluations*

European Union (http://ecb.jrc.it/esis/)
International Agency for Research on Cancer (IARC) (http://www.iarc.fr)
World Health Organization (http://www.euro.who.int/healthtopics)
US Department of Health and Human Services (DHHS) which releases the Report on Carcinogens (RoC) (http://ntp.niehs.nih.gov/ntp/roc/toc11.html)
US Enviromental Protection Agencies (http://cfpub.epa.gov/ncea/iris/index.cfm)
Gesellschaft Deutscher Chemiker (GDCh) German Advisory Committee on Existing Chemicals (http://www.hirzel.de/bua-report/)
Deutsche Forschungsgemeinschaft (DFG) the German Commission for the Investigation of Health Hazards of chemical compounds in the work area (http://www.dfg.de/en/index.html)
American Conference of Governmental Industrial Hygienists (ACGIH) (http://www.acgih.org)
National Institute for Occupational Safety and Health (NIOSH) (http://cdc.gov/niosh/)

tal Protection Agency (USEPA) parameters for non-carcinogenic effects: reference concentrations for inhalation (RfCs) and reference doses for ingestion (RfDs). Exposure limits for food additives by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and Pesticides Residues (JMPR) are also presented. Other relevant parameters are also reported;

- ***restriction of marketing and use.*** This subsection provides information whether a substance (as individual or as a member of a group of substances) is submitted to restrictions according to regulations issued by the Italian government or by the European Union mainly in the context of Marketing and Use Restrictions Directive (Council Directive 76/769/EEC).

11. Hazard classifications: this section includes the complete European Union Hazard Classification according to Directive 67/548/EEC. It is subdivided in:

- ***classification*** (including hazard category(ies) and risk phrases);
- ***concentration limits for the classification of dangerous preparation.*** Specific concentration limits for substances contained in preparations are given for those substances for which it is scientifically proven that specific effects occur at concentrations different than the generic concentration limits given in the preparation Directive (1999/45/EC);
- ***Adaptation to technical progress (ATP)***, the last EC legislative measure (Adaptation to technical progress) by which the substance is classified, regardless of the formal national act of implementation. This information allows to date the classification and it is particularly useful in the case of different classifications made by different institutions. The last Adaptation to technical progress was the 29th, introduced by Directive 2004/73/EC dated 29 April 2004 [8].

12. National and international classifications and evaluations. The section contains an overview of selected carcinogenicity classifications and evaluations proposed by regulatory Government organizations such as the US Environmental Protection Agency (USEPA) and the US Department of Health and Human Services (US DHHS), national advisory agencies and commissions, such as the Italian Commissione Consultiva Tossicologica Nazionale (CCTN) and the National Institute for Occupational Safety and Health (NIOSH), international independent scientific institutions such as the International Agency for Research on Cancer (IARC), the World Health Organization (WHO), the International Programme on Chemical Safety (IPCS), and other evaluations performed by different institutions such as the European Environmental Toxicology Centre (ECETOC) *(Table 2)*. These evaluations are not legally binding but represent a scientific reference in handling environmental issues.

12.1 International Agency for Research on Cancer (IARC). The subsection presents IARC summary evaluations including:

- degree of evidence for carcinogenicity in humans. The following standard descriptors of the levels of evidence are used: sufficient evidence of carcinogenicity; limited evidence of carcinogenicity; inadequate evidence of carcinogenicity; evidence suggesting lack of carcinogenicity;
- degree of evidence for carcinogenicity in experimental animals. The following standard descriptors of levels of evidence are used: sufficient evidence of carcinogenicity, limited evidence of carcinogenicity, inadequate evidence of carcinogenicity, evidence suggesting lack of carcinogenicity;
- carcinogenesis category: the carcinogenic classification adopted by the IARC, based on the description of the epidemiological evidence and a parallel description of the experimental evidence (human carcinogen; probably carcinogenic to humans; possibly carcinogenic to humans; not classifiable as to its carcinogenicity to humans; probably not carcinogenic to humans) is included;
- bibliographic reference: the most recent relevant IARC Monographs. All previous IARC Monographs are included in section 13 [9].

12.2 National Toxicological Advisory Committee (CCTN). Carcinogenesis category adopted by the National Toxicological Advisory Committee. The CCTN last evaluations were carried out up to 2001 because the Committee was no longer active after this date.

12.3 Report on Carcinogens (RoC). The section includes the carcinogenesis category adopted for the substance as individual chemical substance or part of groups of chemicals as *known*, or suspected carcinogens *(reasonably anticipated to be a human carcinogen)* (*e.g.* dyes metabolized to 3,3'-dimethoxybenzidine or dyes metabolized to benzidine) according to 11th RoC [10].

12.4 Environmental Protection Agency. The subsection includes:

- carcinogenesis category established by the USEPA in accordance with the *Guidelines for carcinogen risk assessment* published for the first time in 1986 [11], revised in 1996 [12] and 1999 [13], and finally in 2005 [14]. INSC takes into consideration substances included in the database Integrated Risk Information System (IRIS) containing downloadable cancer health hazard information for approximately 540 substances [15]. Data are obtained via the USEPA website (www.epa.gov/iris/subst/);
- as a consequence of the development of the new USEPA *Guidelines for carcinogen risk assessment*, for several substances contained in IRIS the assessments performed using the 1986 available guidelines but also in accordance to the 1996 proposed guideline or under the review draft for

1996 and/or the final 2005 guidelines are reported. Therefore, for the same substance, classification according respectively to the old and the new guidelines are available in the INSC (*e.g.,* 1,1-Dichloroethylene (1,1-DCE) classified as a *possible human carcinogen* (Group C) under the 1986 cancer guidelines (USEPA, 1986) [5] and for which, under the draft revised guidelines for carcinogen risk assessment (USEPA, 1999) [6], USEPA concludes that "1,1-DCE exhibits suggestive evidence of carcinogenicity but not sufficient evidence to assess human carcinogenic potential following inhalation exposure in studies in rodents and that the data for 1,1-DCE are inadequate for an assessment of human carcinogenic potential by the oral route" [15];
- quantitative carcinogenic risk assessments. Moreover, in section 12 the qualitative classifications and evaluations previously described are often followed by quantitative evaluation (*e.g.,* oral slope factors, inhalation unit risks, and the doses/concentration levels estimated to induce extremely low risk levels, 10^{-4}; 10^{-5} and 10^{-6}).

Moreover, section 12 includes other evaluations and conclusions such as: evaluations and conclusion by the IPCS-WHO (International Programme on Chemical Safety) comprehending:
- the *evaluation on health and environmental effects* proposed by CICADs (Coincise International Chemical Assessment Documents) including: *hazard identification and dose-response assessment* and
- *criteria for setting tolerable intakes and guidance values and evaluation of risks for human health and the effects on the environment* reported in the EHC (Environmental Health Criteria).

13. Bibliographic references: all reported data are followed by bibliographic references, allowing the consultation of the original sources. This section represents a particular quality aspect of the data bank as it also serves as a portal of factual resources available for each substance. The section indeed gives a list of factual resources available and accessible, generally on free of charge web, allowing users to identify many of the most relevant governative pertinent and relevant documents and monographs *(Table 3)* available for the substance. Three different types of bibliographical references, are available:
- ***basic bibliography:*** all the manual and computerized sources systematically consulted (handbooks, factual data banks, monographic series, technical reports);
- ***specific bibliography:*** bibliographic references, listed in alphabetical order cited only once in the sheet/card and specific for each substance and field of interest (generally articles from scientific reviews, legal notices, technical reports);
- ***cited but not consulted bibliography:*** generally reviews, specific articles, monographs and reports concerning the substance for which only bibliographic coordinates are reported. This file is periodically updated taking into account the releases of international agencies and organization.

14. Updating: all data updating are recorded in chronological order and for each entry updating process the date and the section(s) updated are reported. For each updating the names of persons responsible for are reported in the same section.

DATA GATHERING

Data gathering is made by a standard procedure consisting of consultation of a broad standard set of information sources, selection of data and organization in a format.

Single sources of biomedical and environmental data generally do not include all the information needed for a comprehensive evaluation. It is usually necessary to review several primary as well as secondary information sources to obtain adequate overall data.

Table 3 | *Information sources types used by the Inventario Nazionale delle Sostanze Chimiche (INSC)*

Handbooks, basic references sources and data compilations (*e.g.* Merck Index; Bretherick's Handbook of Reactive Chemical Hazards. 6th edition, 1999; CRC Handbook of Chemistry and Physics. 88th edition, 2007-2008; Dangerous Properties of Industrial and Consumer Chemicals,1994; Patty's Industrial Hygiene and Toxicology. Fifth edition, 2001; Sax's Dangerous Properties of Industrial Materials. 11th Edition, 2007)
Chemical dictionaries (*e.g.* CHEMID (http://chem.sis.nlm.nih.gov/chemidplus/); Registry File of Chemical Abstract (www.cas.org); Chemfinder (http://chemfinder.cambridgesoft.com/); ECICS ((http://ec.europa.eu/taxation_customs/common/databases/ecics/index_en.htm); ESIS (http://ecb.jrc.it/esis/)
Monographs and series published by national and international organizations (BUA Report, IARC monographs, NTP Technical Report, ECETOC Technical Report and Joint Assessment of Commodity Chemicals, Environmental Health Criteria; CICAD)
Journals and periodics
Reports of courses, workshops, proceedings of meetings and congresses
Confidential unpublished reports and grey literature
Exchange-documents between Governments and Organizations (OECD, EU, WHO, NATO)
Internet accessible free of charge or by payment factual data banks and bibliographic databases

The various information sources are generally addressed to specific topics of competence of the institutions who present the data. Therefore, in order to obtain complete information, it is usually necessary to consult all the available information systems dealing with the topic of interest.

Generally, the most complete screening data sets are available for agricultural chemicals and pesticides, pharmaceutical drugs, additives and some other environmental chemicals. For these categories of substances proprietary information are available. These relevant and useful studies, are generally confidential, non published in the open scientific literature and cannot be accessed. Regulatory agencies, such as USEPA Office of Pesticide Programs (OPP) in the context of Pesticide Registration (reported in the Pesticide registration status site www.epa.gov/pesticides/reregistration/status.htm) or WHO, in the framework of Joint Meeting FAO/WHO, use this proprietary information for their evaluation while other, such as IARC, use only information published in the open literature and does not consider proprietary information.

INSC sources include both manual and electronic sources. *Table 3* presents some of the information sources mostly consulted in INSC activities.

Manual sources

The manual sources consist in books, handbooks, safety data sheets, reports, reviews, monographs, directories, data lists and, in general, scientific literature in the specific field under examination.

The INSC structure includes a selected library, containing a large number of books, reports, papers and documents. Past experiences have indicated that the immediate availability at local level of a selected set of manual sources is essential, in particular in the case of emergencies, when information has to be collected in a very short time and the access to the central library may be difficult.

Of particular interest for INSC activities are various publication produced by international organizations, which have a major role in toxicology, environmental toxicology, ecotoxicology, health protection and chemical safety. Typical examples are:

- ***monographs and documents*** produces for specific substances by the IPCS (International Programme on Chemical Safety) and aimed at implementing activities related to chemical safety. These include EHC (Environmental Health Criteria Documents) and CICAD (Concise International Chemical Assessment Documents);
- ***monographs and evaluations*** prepared by the JECFA (WHO/FAO Joint Expert Committee on Food Additives) (www.inchem.org/pages/jecfa.html) including food additives as well as contaminants in foods, residues of veterinary drugs in food, naturally occurring toxicants and the JMPR (WHO/FAO Joint Meeting on Pesticide Residues) (www.inchem.org/pages/jmpr.html)
- ***monographs series*** produced by the IARC (International Agency for Research on Cancer) (www.iarc.fr).

Moreover, also:

- ***BUA Report*** series produced by *GDCh* (Gesellschaft Deutscher Chemiker) Advisory Committee on Existing Chemicals (abbreviation BUA) which utilize published scientific literature as well as data from industry (www.hirzel.de/bua-report/);
- ***RED*** (Registration Eligibility Decision) documents issued by USEPA OPP. RED documents containing human health and ecological risk assessments and EPA decisions on pesticides subjected to re-registration (review of old pesticides, initially registered prior to 1984, to ensure that they meet current scientific and regulatory standards) (www.epa.gov/pesticides/reregistration/status.htm);
- ***Toxicity Profiles*** produced by BIBRA (British Industrial Biological Research Association) an international and critical review of the most pertinent toxicological data published on commercially important chemicals (www.bibra-information.co.uk/toxicity_profiles_overview.html);
- ***Toxicological Profiles*** produced by ATSDR (Agency for Toxic Substances and Disease Registry) of the US Department of Health and Human Services for chemicals found at hazardous waste sites (www.atsdr.cdc.gov/);
- ***Fiches Toxicologiques*** developed by the French INRS (Institut National de Recerche et de Securité) that report a summary of health and safety information about specific chemical agents or groups of chemicals (www.inrs.fr);
- ***documents published by the ECETOC*** (European Centre for Ecotoxicology and Toxicology of Chemicals), a scientific, non-profit association, financed by 50 of Europe's leading chemical-related companies which co-operates with governmental agencies and other organisations concerned with the effects of chemicals on health and the environment. ECETOC publishes a range of reports varying in scope from the *Technical Reports* on specific chemicals to *Joint Assessment of Commodity Chemicals* (JACC), dealing with chemicals produced in large tonnage by several companies and having widespread and multiple uses (www.ecetoc.org);
- ***HERA (Human and Environmental Risk Assessment)*** risk assessments conducted on chemicals used in household cleaning products. HERA is a European voluntary initiative launched in 1999 by AISE (International Association for Soaps Detergents and Maintenance Products), representing the formulators and manufacturers of such products and CEFIC (European Chemical Industry Council), representing the suppliers and manufacturers of the raw materials (www.heraproject.com/)

Presently, data reported by manual sources are also available from computerized sources, here after mentioned.

Moreover, it is worthwhile noticing that while many sources of information deal with specific matters, others are multidisciplinary. For example CHEMID

data bank (http://chem.sis.nlm.nih.gov/chemidplus/) or CAS REGISTRY files (www.cas.org) deal exclusively with identification (providing data on nomenclature, synonyms, CAS numbers, formulas, isomers and related compounds), GENTOX (Genetic Toxicology Data Bank) (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?GENETOX) deals specifically with genotoxicity while DART (Developmental and Reproductive Toxicology) (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?DARTETIC) evaluate developmental toxicity of environmental agents. Other sources, such as *IARC Monographs* or *Technical Reports of the National Toxicology Program* (http://ntp.niehs.nih.gov/) although giving particular attention to specific end-points, such as carcinogenesis, provide complete reviews on the considered substance taking into account all the data relevant to substance toxicity including data on physical and chemical properties, analytical methods, sources of exposure, animal toxicity, epidemiological studies, kinetics and metabolism. The Hazardous Substances Data Bank (HSDB) (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB) equally investigate different matters such as physical and chemical properties, reactivity, toxicity, ecotoxicity and environmental impact.

Electronic sources

Information from primary literature can easily be obtained online through a search in:

- ***factual data banks*** containing pre-selected factual information. Data are organized in the form of summaries completed with bibliographic references and searchable by toxic chemicals;
- ***bibliographic databases*** providing direct access to the literature without any pre-selection and used for exhaustive searches when factual databases contain insufficient data. Examples of some relevant factual and bibliographic data banks routinely used by INSC are listed in *Table 4*.

In the procedure of data gathering factual sources, handbooks and data banks are used as primarily sources of data but because both are usually "secondary data sources" the original data source is often checked and directly consulted if available or retrieved through a bibliographic data banks query. This sometimes happens also in case of disagreement for the same data (particularly in the case of numerical data such as physical-chemical properties or toxicological parameters) reported in different sources. In general, data should be *adequate*. The adequacy is defined by two basic concepts, reliability and relevance:

- *reliability*, covering the inherent quality of the data. The concept of reliability includes *credibility* of the original sources and implicitly of the author/agency proposing the data and *precision* of the data which is directly linked/related to *accuracy* in particular for numerical data;
- the second concept is the *relevance* of the data which is directly linked/related to relevance *i.e.* if the data is suitable, appropriate and relevant to the goal. Credibility may be achieved through transparency

Table 4 | *Some data banks and bibliographic databases*

AQUIRE (Aquatic Toxicity Information Retrieval) Producer: US Environmental Protection Agency (EPA) Content: Aquatic Toxicity Information bibliographic Accessibility: charged, through STN network
AGRICOLA (Agriculture Online Access) Producer: National Agricultural Library (NAL), USA Content: Food, agriculture and related fields bibliographic Accessibility: charged, through STN network
BEILSTEIN Producer: Beilstein GmbH Content: structure and factual database in organic chemistry factual Accessibility: charged, through STN network
BIOSIS Producer: Thomson Scientific, UK Content: Biosciences/Biomedical bibliographic Accessibility: charged, through STN network
CHEMICAL ABSTRACT REGISTRY FILE Producer: Chemical Abstracts Service (CAS), USA Content: structure and identification Chemical dictionaries Accessibility: charged, through STN network
ECICS (European Customs Inventory of Chemical Substances) (http://ec.europa.eu/taxation_customs/common/databases/ecics/index_en.htm) Producer: European Commission Content: identification Chemical dictionaries Accessibility: free of charge, through European Commission network
EMBASE (Excerpta Medica) Producer: Elsevier BV, The Netherlands. Content: literature on biomedical and pharmaceutical fields bibliographic Accessibility: charged, through STN network
HSDB (Hazardous Substances Data Bank) Producer: National Library of Medicine's Toxicology Information Program, USA Content: information on toxicology and the environmental effects of chemicals factual Accessibility: free of charge, through TOXNET
MSDS-CCOHS (Material Safety Data Sheets from the Canadian Centre for Occupation Health and Safety) Producer: Canadian Centre for Occupational Health and Safety, Canada Content: data sheets containing health and safety data factual Accessibility: charged, through STN network
MSDS-OHS (OHS Material Safety Data Sheets) Producer: MDL Information Systems, Inc., USA Content: data sheets containing health, safety, and environmental data factual Accessibility: charged, through STN network
NTP (National Toxicology Program) Producer: Content: peer reviewed data bases with short term toxicity, organ system toxicity and carcinogenic data factual Accessibility: free of charge, through NTP
RTECS (Registry of Toxic Effects of Chemical Substances) Producer: MDL Information Systems, Inc., USA Content: toxicity data factual Accessibility: charged, through STN network

and competence and this necessarily implies the possibility to retrieve the original data which therefore must be always fully bibliographically referenced. The problem of quality of data is often found particularly with the so called *existing chemicals* for which there is a wide availability of data, sometimes excessive, but generated prior to the GLP requirements and the standardisation of testing methods. These data can be used but they require an evaluation concerning their reliability.

Portals

Today there is also a large availability of "portals" easily accessible which offer free public access to information on properties of chemicals allowing for simultaneous search of multiple databases and providing clearly described sources and quality of data contained. Particularly, INSC refers mainly and usually to the following:

- ESIS (European chemical Substances Information System) (http://ecb.jrc.it/esis/) serves as a portal to the existing chemicals data sets maintained by ECB (European Chemicals Bureau). ESIS provides information on chemicals, related to: EINECS (European Inventory of Existing Commercial Substances); ELINCS (European List of Notified Chemical Substances); List of EU HPVCs (High Production Volume Chemicals) and LPVCs (Low Production Volume Chemicals); IUCLID chemical datasets; EU Priority substance risk assessment reports and Harmonised classification and labelling;
- TOXNET (Toxicological Data Network) (http://toxnet.nlm.nih.gov/) a cluster of factual and bibliographic databases on toxicology, hazardous chemicals and related areas developed by the National Library of Medicine. In particular the following are used: HSDB, CCRIS (Chemical Carcinogenesis Research Information System), GENTOX, HAZMAP;
- NTP (National Toxicology Program) (http://ntp.niehs.nih.gov/) in the section Studies Results and Research Project provides the access to the results of NTP studies while the section Public Health links to the Report on Carcinogens (RoC);
- INCHEM from IPCS (www.inchem.org/) provides a collection of chemical-safety information from intergovernmental organizations. The collection includes the established series of the reports of the JMPR, the JECFA, EHC, CICAD, IARC Summaries and Evaluations, IPCS-ICSC (International Safety Cards) and IPCS Poisons Information Monographs.

In the above mentioned list of data sources also the so-called "grey literature" has to be included, which means unpublished technical data in the form of reports or provisional document concerning effects on health and the environment of certain chemicals.

Data gathering is free of charge from some sources such as TOXNET, ESIS, NTP, INCHEM database, while the use of CAS REGISTRY file, RTECS and the most of bibliographic databases except for PubMed is associated with a cost which is variable, for example, in case of subscription or in relation to query time.

New sources are continuously added to the list of standard sources such as MAK and ACGIH, electronic and papery sources yearly updated, Pesticide Manual or The Merck Index reference books new editions and all the new monographic series of IARC or EHC.

CRITERIA FOR THE INCLUSION IN INSC

According to the original project elaborated by a working group charged to assess the feasibility of a national inventory, the objective was to provide ready-to-use relevant information in each situation where chemical substances are involved.

The substances covered by the INSC are individual chemicals and include solvents, chemical intermediates, environmental pollutants, pesticides, ozone depleting substances, aromatic amines, chemical weapons and their precursors and generally all those substances which might pose concern to man and the environment.

At the present time INSC contains information on more than 3000 substances and for about 2000 substances raw data are available, consisting of bibliographic references, specific articles collected in the open and grey literature, chemicals monographs. This electronic dossier is kept easily available and updated in view of the preparation of a computerized data sheet.

Taking into account the differences among the INSC users, categories originally excluded from the scope of INSC are at present included. This is the case of medicinal products for human or veterinary use, or food or feedingstuffs or food additives or flavouring substances.

UPDATING THE INSC

Online databases are generally updated on regular basis.

INSC is usually updated periodically on a case by-case basis according to the specific requests made by the users.

In addition specific sections (such as EU classification according to Directive 67/548/EEC; IARC, NTP and USEPA evaluation, and TLV values) are regularly updated systematically taking into account both new EU legislations (new updating of Annex I) and new published evaluations.

USERS OF THE INSC

The INSC is an information service for the public health institutions responsible for the control of exposure to chemicals and application of pertinent legislation; it is not a commercial data bank *(Table 5)*.

As already said, the original objective of INSC was to systematically store information on substances of

Table 5 | *Main users of the INSC*

National bodies: institutions operating at the central level:
- National Institute of Health (ISS);
- National Institute of Occupational Safety and Prevention (ISPESL);
- Experimental Zooprophylactic Institutes (IIZZSS);
- Ministry of Health and other Ministries (Environment, Land and Sea; Cultural Heritage and Activities; Labour, Transport).
- Italian National Research Council (CNR)
- Regional (ARPA) and Provincial (APPA) Environmental Protection Agencies
Other national institutions
- National Agency for the Protection of the Environment and the Technical Services (APAT)
- Universities
Administrative/scientific/technical institutions operating at regional, provincial and municipal level:
- Health Care Offices of Regions and Self-governing Provinces
- Local Health Care Agencies, ASL; Local Health Units (USL);
- Public Hospitals

main interest from toxicological and ecotoxicological point of view.

As the structure of the INSC grew up, it became more evident that its peculiarity was the possibility of a direct interaction with the users, in order to modulate the quality and quantity of the information collected as a function of the actual needs of the peripheral bodies of the National Health Service. At present INSC is an interactive structure totally open to users. The user profile is multidisciplinary. Once a specific problem arises, specific or generic information is gathered depending upon the request.

INSC ACTIVITIES

The activities of the INSC are organised into the following areas:

- answers to ISS personnel;
- answers to external users *(Table 5)* for different purposes which always imply, independently from the query, the updating of a standard set of information (such as: identification, uses, acute toxicity, physico-chemical properties, classification, evaluation/assessment, bibliography);
- regularly updating taking into account community legislation (updatings of Annex I of Directive 67/548/EEC in terms of updating and new entrance) and new published evaluations. In particular the database is updated in the occurrence of the publication of new IARC Monographs, new Reports on Carcinogens by the DHHS.

PROJECTS RUNNING AT INSC

Data banks on specific matters are developed starting from INSC data and experience. Among them:

- the Carcinogenic Data Bank (BDC) containing carcinogenicity evaluations/classifications produced by European Union and by other institutions (IARC, USEPA, NTP, CCTN);
- the Data Bank on Sensitizing substances (BDS) providing concise and non-confidential information on sensitizing or potentially sensitizing agents;
- the Reclamation Data Bank containing reference limit values for the substances mainly found in contaminated soils (quality standards) and underground waters.

SOME CONCLUSIONS

The INSC activity started in a time period characterized by accidental events, new risks identification, new European Union's initiatives, directives, recommendations, and difficulties in finding the relevant information. In that period the information was mostly obtained consulting books, scientific journals and reports, evaluations produced by important relevant institutions, without the help of online computerized information. It has been a hard work, but the gratitude received by many users has given a remarkable satisfaction to the involved personnel.

Submitted on invitation.
Accepted on 16 December 2007.

Acknowledgements

This paper is dedicated to Angelo Sampaolo who has created the INSC and personally contributed to its evolution and to Giovanni A. Zapponi who has given to INSC invaluable and ever enthusiastic guidance, scientific expertise, encouragement and support. We wish also to express our deep appreciation and thanks to all who work in the INSC throughout the years.

References

1. European Community. Council Directive 82/501/EEC of 24 June 1982 on the major-accident hazards of certain industrial activities. *Official Journal of the European Communities* L 230, 5/8/82.
2. Pocchiari F, Silano V, Zapponi GA. The chemical risk management process in Italy. A case study: the Seveso accident. *Sci Total Environ* 51:227-35.
3. Sampaolo A. 1990 L'Inventario Nazionale delle Sostanze Chimiche. *Ann Ist Super Sanità* 1990;26(Suppl.)91-6.
4. Commission of the European Community. Commission Directive 79/831/EEC of 18 September 1979 amending for the 6th time Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (6th amendment). *Official Journal of the European Communities* L 258, 15/10/79.
5. Italia. Legge del 23 dicembre 1978, n. 833. Istituzione del Servizio Sanitario Nazionale. Articolo 9. *Gazzetta Ufficiale* n. 360, 28 dicembre 1978.
6. Council of the European Economic Community. Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Official Journal of the European Communities* L 196/1, 16/8/67.

7. Caroli S, Violante N. Outline of the ISS code for the classification of chemical substances for use in compiling a National Inventory. *Ann Ist Super Sanità* 1991;27(2).
8. Commission of the European Communities. Commission Directive 2004/73/EC of 29 April 2004 adapting to technical progress for the 29th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Official Journal of the European Union* L 216/3, 16/6/2004.
9. International Agency for Research on Cancer. *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans.* Volume 1 to 91. Lyon; IARC: 1972-2008.
10. National Toxicology Program. *Report on Carcinogens.* 11. ed. US Department of Health and Human Services, Public Health Service, 2005.
11. US Environmental Protection Agency. Guidelines for carcinogen risk assessment (EPA/630/R-00/004). *Fed Reg* 1986; 51(185):33992-4003.
12. US Environmental Protection Agency. Proposed guidelines for carcinogen risk assessment (EPA/600/P-92/003C). *Fed Reg* 1996;61(79):17960-8011.
13. US Environmental Protection Agency. *Guidelines for carcinogen risk assessment*. Risk Assessment Forum. Washington DC; USEPA; 1999. (Review Draft, NCEA-F-0644, July 1999).
14. US Environmental Protection Agency. 2005. *Guidelines for carcinogen risk assessment*. Washington DC: USEPA; 2005. (EPA/630/P-03/001F, Mar 2005).
15. US Environmental Protection Agency. 2008 *Integrated Risk Information System*. Washington DC: USEPA, Office of Research and Development, National Center for Environmental Assessment. Available from: www.epa.gov/iris/index.html.