The ISS Carcinogens Data Bank (BDC)

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Summary. The Data Bank on Carcinogens (*Banca Dati Cancerogeni*, BDC) is a factual data bank, available on the Istituto Superiore di Sanità website, aimed at supporting the risk management decision making of central and local administrators. It can also represent a valuable tool for industry. The available information on carcinogenicity evaluations/classifications produced by European Union and by other institutions (IARC, USEPA, NTP, CCTN) is presented in a concise form accompanied by bibliographic references enabling the users to consult the original sources and, in some cases, to be directly connected to the relevant website. The classifications carried out by each organization in accordance with its own criteria assign the examined agents to specific qualitative categories and do not include quantitative assessment. BDC intends to provide an easy tool for experts, researchers and risk managers dealing with carcinogenic agents.

Key words: data bank, carcinogenic agents, classification, evaluation.

Riassunto *(La Banca Dati Cancerogeni)*. La Banca Dati Cancerogeni (BDC) è una banca dati fattuale disponibile sul sito web dell' Istituto Superiore di Sanità ed ha lo scopo di supportare le fasi decisionali della gestione del rischio da parte di amministratori a livello centrale o locale. La BDC può anche rappresentare un valido strumento per l'industria. L'informazione disponibile, relativa a valutazioni/classificazioni di cancerogenicità dell'Unione Europea e di altre istituzioni (IARC, USEPA, NTP, CCTN), è presentata in forma sintetica ed è accompagnata da riferimenti bibliografici che consentono di risalire alla fonte originale e, in alcuni casi, di connettersi direttamente al sito web corrispondente. Le classificazioni prodotte da ciascuna organizzazione in accordo ai propri criteri inseriscono ciascuna sostanza considerata in categorie qualitative e non includono una valutazione quantitativa. La BDC intende fornire uno strumento di semplice utilizzo a esperti, ricercatori e *risk manager* che si occupano di agenti cancerogeni.

Parole chiave: banca dati, agenti cancerogeni, classificazioni, valutazioni.

INTRODUCTION

The evaluation and classification of carcinogenic agents is carried out at international level mainly by the European Union (EU) and the International Agency for Research on Cancer (IARC, a scientific independent institution). In the United States, the Environmental Protection Agency (USEPA) has a major role in this matter, together with the US National Toxicology Program (NTP) of the Department of Health and Human Services (US DHHS), the latter with regulatory purpose. In Italy the evaluation and classification of carcinogenic agents was at care of the National Toxicological Advisory Committee (CCTN) (national consulting organization) until 2001.

It is worthwhile noticing that most of regulatory agencies consider the agents classified by IARC for inclusion in their own list of carcinogens (*e.g.,* Canada, USA, Denmark, Finland) [1].

The classifications, carried out by the proponent organization in accordance with its clearly specified criteria and procedures, assign the examined agents to specific qualitative categories, on the basis of the overall evidence of carcinogenicity emerging from epidemiological studies, long-term experimental studies on laboratory animals and other relevant data (chemical properties, metabolism, genetic effects, structure/activity relationship etc.). These schemes are qualitative and generally refer only to the "weight of evidence" or "level of evidence" or "degrees of strength of the evidence" of the carcinogenicity related to an exposure; the classification does not include any "carcinogenic potency" quantitative assessment [2].

The classification systems adopted by the different organizations or institutions are reported in *Table 1*.

Some of the above institutions (*e.g.,* European Union) distinguish three categories (*i.e.,* human carcinogens, animal carcinogens and suspected carcinogens respectively) while other systems distinguish two

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Table 1 | *Categories, group and descriptors developed by organizations and institutions involved in classification and evaluation of carcinogenic agents*

European Union (Directive 67/548/EEC) [3]	
Cat. 1	Substances known to be carcinogenic to man
Cat. 2	Substances which should be regarded as if they are carcinogenic to man
Cat. 3	Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment
International Agency for Research on Cancer (IARC) [4]	
Group 1	The agent is carcinogenic to humans
Group 2A	The agent is probably carcinogenic to humans
Group 2B	The agent is possibly carcinogenic to humans
Group 3	The agent is not classifiable as to its carcinogenicity to humans
Group 4	The agent is probably not carcinogenic to humans
US Environmental Protection Agency (Guidelines for Carcinogen Risk Assessment 1986) [5]	
Group A	Human carcinogen
Group B1	Probable human carcinogen - based on limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals
Group B2	Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals
Group C	Possible human carcinogen
Group D	Not classifiable as to human carcinogenicity
Group E	Evidence of non-carcinogenicity for humans
US Environmental Protection Agency (proposed Guidelines for Carcinogen Risk Assessment 1996) [6]	
Known/likely human carcinogen	
Carcinogenic potential cannot be determined	
Not likely to be carcinogenic to humans	
US Environmental Protection Agency (Guidelines for Carcinogen Risk Assessment 1999) [7]	
Carcinogenic to humans	
Likely to be carcinogenic to humans	
Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential	
Data are inadequate for an assessment of human carcinogenic potential	
Not likely to be carcinogenic to humans	
US Environmental Protection Agency (Guidelines for Carcinogen Risk Assessment 2005) [8]	
Carcinogenic to humans	
Likely to be carcinogenic to humans	
Suggestive evidence of carcinogenic potential	
Inadequate Information to assess carcinogenic potential	
Not likely to be carcinogenic to humans	
US National Toxicological program (NTP) Report on Carcinogens [9]	
R	Reasonably anticipated to be a human carcinogen
K	Known to be a human carcinogen

categories (US DHHS in Report on Carcinogens, RoC) while USEPA and IARC establish five categories. CCTN adopted the categories of the EU but added three other categories; USEPA, IARC and CCTN have also adopted the category of *lack of evidence of carcinogenicity (Table 1)*.

The assignment to the classification categories may sometimes be not identical, due to differences among the principles adopted and the parameters considered by the various institutions. In particular, important differences exist in the criteria adopted for the selection of the databases to be used for classification. For instance, since the beginning in 1972, the IARC Monographs have adopted the procedure to base their evaluations only on primary information published in the open, peer-reviewed literature and on national governments' reports, which are freely available for consultation, plus articles accepted for publication. This procedure is recently confirmed [10]. EU use also "confidential" information not available to the general public, like some programmes of the World Health Organization (*e.g.*, FAO-WHO joint Meeting on toxicity of pesticides and pesticide residues); other international organizations use proprietary information of limited diffusion (*e.g.,* data produced by involved industries), to carry out their evaluations. In these cases, a main weight is given to the respect of good laboratory practices (GLP) and to the quality of the studies independently by their diffusion.

In fact for many chemicals, in particular pesticides, most relevant and basic information is found in unpublished studies submitted by the proponent as part of the registration package.

Lastly, also *expert judgment* is exercised when scientific basis is not easily comprehensible and/or when the data on carcinogenic chemicals are not sufficiently detailed, and when a precise elucidation of the mechanism of action of the carcinogen or the complete pathophysiological process for development of tumours in animals or humans must be taken into account. The *expert judgment* may include a subjective opinions that can lead to evaluations that may differ among expert groups of different Agencies and also among members or group of experts of a same Agency [1]. So, different Agencies may produce carcinogenesis classifications that are not fully overlapping for the same substance, as already mentioned. This of course derives from the differences in the objectives and endpoints of the different Agencies and from the different procedures followed [11, 12].

For example, RoC lists Direct Black 38 and Direct Blue 6 (in the group of Benzidine Dye Class) as *known to be human carcinogens* even if there is no direct epidemiological evidence to support this assessment [9] while IARC classifies both (Benzidine-Based Dyes) as *probably carcinogenic to humans* (Group 2A) on the basis of sufficient evidence for carcinogenicity in experimental animals and inadequate evidence in humans [13].

In some cases, even if the available human epidemiological evidence is not sufficient to establish a causal relationship between the exposure to the examined agents and cancer in humans, different criteria may be adopted. An example is provided by the ethylene oxide (ETO) which has been upgraded by the IARC from the 2A to 1 Groups, based on mechanistic and other relevant data (ETO is an alkylating agent, which means that it places an alkyl chemical group on the DNA and induces genetic mutations and chromosomal breakage in a wide range of species) [14]. Also 2,3,7,8-tetrachlorodibenzo-para-dioxin (dioxin), for which the evidence of carcinogenicity in humans is limited, has been upgraded from 2A to 1 based on the supporting evidence from other relevant data (dioxin is a multi-site carcinogen in experimental animals that acts through a receptor-mediated mechanism in cells that are believed to be common to animals and humans) [15].

However, the above mentioned differences in the carcinogenicity classification are generally limited and classifications are mostly comparable, so that no significant problems arise for the classification users. Moreover the joint examination of the evaluations carried out by different institutions, even if sometimes not completely overlapping, may provide a more complete view to the end users. For this completeness need, the BDC (Carcinogens Data Bank) includes the evaluations by various institutions and not only a single one. The time period in which such classifications are produced allow the readers to consider them in the temporal context (*e.g.*, recent or less recent).

OBJECTIVE

At present, according to Directive 67/548/EEC, European Union officially classified approximately 2700 "existing" substance entries (*i.e.* listed in the European INventory of Existing Commercial chemical Substances – EINECS – that contains 100 204 substances), and 1100 "new" substance entries (*i.e.,* listed in the European LIst of Notified Chemical Substances – ELINCS) corresponding to about 8000 individual substances with harmonized classification [16-18].

In the Annex I to Directive 67/548/EEC the term entry defines both single substances or groups of substances *(Table 2)*. For example, the entry *Chromium (VI) compounds*, includes 56 single chromium compounds listed in the EINECS inventory. Each *Chromium (VI) compound*, with the exception of those specified in the Annex I *(Table 3)*, is covered by the group classification. Since the Annex I contains more than 80 entries *(Table 2)* to which the group classification applies, the number of classified individual substances is consequently much higher than the number of the entries in Annex I.

However, the number of substances potentially dangerous is anyway significantly higher than the number of those officially classified, due to the complexity of the classification procedures adopted by the working group. Therefore, substances not yet officially classified but potentially classifiable as dangerous, are submitted to the obligation of *self-classification*.

In fact, the Article 6 of the seventh amendment to Directive 67/548/EEC (Directive 92/32/EEC) requires that manufacturers, distributors and import-

Table 2 | *Carcinogenic group entries listed in Annex I to Directive 67/548/EEC [16]*

Index number	Group name	Number of substances in the EINECS
004-002-00-2	Beryllium compounds with the exception of aluminium beryllium silicates, and with those specified in the Annex I **Carc. Cat. 2; R49** | *T+; R26* | *T; R25-48/23* | *Xi; R36/37/38* | *R43* | *N; R51-53*	33
024-017-00-8	Chromium (VI) compounds, with the exception of barium chromate and of compounds specified in the Annex I **Carc. Cat. 2; R49** | *R43* | *N; R50-53*	56
611-024-00-1	Benzidine based azo dyes **Carc. Cat. 2; R45**	10
611-029-00-9	o-Dianisidine based azo dyes **Carc. Cat. 2; R45**	49
612-009-00-2	Salts of aniline **Carc. Cat. 3; R40** | *Muta. Cat. 3; R68* | *T; R23/24/25* | *Xi; R41* | *R43* | *N; R50*	14
033-005-00-1	Arsenic acid and its salts **Carc. Cat. 1; R45** | *T; R23/25* | *N; R50-53*	33
007-014-00-6	Salts of hydrazine **Carc. Cat. 2; R45** | *T; R23/24/25* | *R43* |*N; R50-53*	9

Table 3 | *Some specific chromium compounds listed in Annex I to Directive 67/548/EEC [16]*

Index Number	Name	Classification
024-001-00-0	Chromium (VI) trioxide	O; R9 ***Carc. Cat. 1; R45*** Muta. Cat. 2; R46 Repr. Cat. 3; R62 T+; R26 T; R24/25-48/23 C; R35 R42/43 N; R50-53
024-010-00-X	Dichromium tris(chromate)	O; R8 ***Carc. Cat. 2; R45*** C; R35 R43 N; R50-53
024-006-00-8	Potassium chromate	***Carc. Cat. 2; R49*** Muta. Cat. 2; R46 Xi; R36/37/38 R43 N; R50-53
082-004-00-2	Lead chromate	***Carc. Cat. 3; R40*** Repr. Cat. 1; R61 Repr. Cat. 3; R62 R33 N; R50-53
024-003-00-1	Ammonium dichromate	E; R2 O; R8 ***Carc. Cat. 2; R45*** Muta. Cat. 2; R46 Repr. Cat. 2; R60-61 T+; R26 T; R25-48/23 Xn; R21 C; R34 R42/43 N; R50-53

ers of dangerous substances which are registered as existing chemicals in the EINECS but which have not yet been introduced into Annex I, are obliged "to carry out an investigation to make themselves aware of the relevant and accessible data which exist concerning the properties of such substances. On the basis of this information, they shall package and provisionally label these substances according to the classification criteria set up in Annex VI to Directive 67/548" [19]. The arrangement of a self-classification implies a search through *retrieving existing relevant and accessible data* concerning properties of substances [19]. The data do not need to be experimentally produced, but may be obtained by a pertinent literature searching with reference to what is *reasonably known*. The remarkably high amount of scientific information presently available through internet may be of fundamental help. Just for making easier the access to updated and comprehensive information on carcinogenic agents, the Istituto Superiore di Sanità (ISS) decided to produce a freely accessible data bank on the classification/evaluation of carcinogenic chemical agent (Banca Dati Cancerogeni, BDC) available on the ISS website.

A close link exists between self-classification and the downstream consequences within European legislation, such as the Marketing and Use Restrictions Directive (Council Directive 76/769/EEC), the Preparations Directive (Council Directive 1999/45/EC), the Carcinogens in the Workplace Directive (Directive 2004/37/EC) [20] and the Chemical Agents in the Workplace Directive (Directive 98/24/EC) [21].

In particular:

- according to Directive 76/769/EEC no substances or preparations classified as category 1 and 2 carcinogens may be permitted to be placed on the market for use by the general public; and
- the above mentioned chemical agents Directive 98/24/EEC, (implemented at Italian level with the Legislative Decree n. 25/2002), makes reference not only to officially classified substances, but also to any chemical agent which meets the criteria for classification as carcinogenic according to the criteria of Annex VI to Directive 67/548/EEC, whether or not that substance is officially classified under the Directive [21].

BACKGROUND OF BDC

The project of a data bank on carcinogenic agents exists in the ISS since 1994. The first results were published in the occasion of the implementation of carcinogens at work Directive 90/394/EEC [11]. Afterwards, updating were published, always on papery support, in 1996 [22], in 2000 [12] and in 2004 [23].

SOME FEATURES OF BDC

The BDC is a computerized database aimed at supporting the phase of hazard identification and is prepared and maintained by the ISS Section of Dangerous Substances and Preparations within the Department of Environment and Primary Prevention, with the assistance of Sector I – Information Technology of the Information, Documentation, Library and Publishing Activities Service.

This activity obviously involves gathering of available data.

The BDC is a factual data bank, linked to the Italian National Inventory of Chemical Substances (Inventario Nazionale delle Sostanze Chimiche) from which it derives [24]. In the BDC the information is presented in a concise form, immediately usable, providing data as much as possible complete on carcinogenicity evaluations/classifications produced by European Union and by other institutions, charged with this task, at international or national level, accompanied by bibliographic references enabling the users to consult the original sources and, in some cases, to directly be connected to the corresponding website.

For each entry, BDC indicates the presence or lack of information reporting whether the considered sub-

stance has been evaluated or not by the competent institutions.

SELECTION CRITERIA TO INCLUDE AGENTS IN THE DATA BANK

At present, BDC contains approximately 1000 entries of agents that have been considered by different organizations and institutions involved in carcinogenic classification and evaluation.

The term *agent*, according to the IARC definition, includes individual chemical compounds, groups of related chemical compounds, physical agents (such as radiation) and biological factors (such as viruses), environmental pollutants, dyes, chemical intermediates, active ingredient pesticide agents, pharmaceutical drugs, food additives, occupational exposures and processes [10]. At moment the BDC does not include viruses, pharmacological therapies, biological and physical agents, cultural habits, toxins, dietary practices whose evaluation will be afterwards made available.

At present the BDC includes:

- all the substances officially classified by European Union, included in Annex I to Directive 67/548/EEC as carcinogenic in category 1 (substances known to be carcinogenic to man) or category 2 (substances which should be regarded as if they are carcinogenic to man) with symbol "T" and the *risk phrases* R45 (may cause cancer) or R49 (may cause cancer by inhalation) or in category 3 (substances that cause concern for man, as to possible carcinogenic effects; normally there is evidence of toxicity in only one species, and results are variable) with symbol "Xn" and the risk phrase R40 (limited evidence of a carcinogenic effect). At present, Annex I lists 197 entries classified as carcinogens in category 1 (192 with risk phrase R 45 and 5 with risk phrase R 49); 634 entries classified as carcinogens in category 2 (634 with risk phrase R 45 and 9 with risk phrase R 49) and 132 entries classified as carcinogens in category 3. Annex I contains entries for more than 500 petroleum derivatives whose classification was limited to the health hazard of carcinogenicity and aspiration [16];
- substances included in Annex I to Directive 67/548/EEC classified as mutagenic in category 2 (substances which should be regarded as mutagenic to man), with symbol "T" and the risk phrase R46 (may cause heritable genetic damage) or category 3 (substances that cause concern for man for possible mutagenic effects; normally there is evidence of toxicity in only one species, and results are variable) with symbol "Xn" and the risk phrase R68 (possible risk of irreversible effects). Until up today, the 29th Adaptation to Technical Progress (ATP) has been published and 30th and 31st ATPs are in progress. No substances are classified as mutagenic of category 1 [16];
- all agents taken into consideration by IARC monographs and included in one of the following categories: Group 1 (carcinogenic to humans); Group 2A (probably carcinogenic to humans) and Group 2B (possibly carcinogenic to humans); selected agents classified as Group 3 (not classifiable as to its carcinogenicity to humans); all agents classified as Group 4 (probably not carcinogenic to humans). Today, 102 agents have been classified by the IARC as proven carcinogenic to humans (Group 1), 68 as probably carcinogenic to humans (Group 2A), 245 as possibly carcinogenic to humans (Group 2B); 516 as not classifiable as to carcinogenicity in humans (Group 3) and just one substance as probably not carcinogenic to humans (Group 4) [4];
- agents, substances, or exposure circumstances listed as either *known to be a human carcinogen,* or *reasonably anticipated to be a human carcinogen* in the RoC Agents released biennially by the US Department of Health and Human Services (DHHS). The 11th RoC contains 246 entries, 58 of which are listed as known to be human carcinogens and with the remaining 188 being listed as *reasonably anticipated to be human carcinogens* [9];
- at present only few exposure circumstances associated to carcinogenic risk according to IARC and RoC, are included in the BDC;
- agents in the list of *substances for industrial use and production processes*, for which the National Toxicological Advisory Committee (CCTN) of Italy considers that there is convincing evidence of carcinogenicity [25]. The list includes two categories: substances known to be carcinogenic to man and substances which should be regarded as if they are carcinogenic to man. CCTN refers basically to IARC Monographs;
- in addition to the above listed criteria, particular cases are considered such as the polycyclic aromatic hydrocarbons (PAH), aromatic amines and antitumoral drugs. In the first case, BDC includes all 60 PAH evaluated by the IARC, even if the definitive monograph is not yet published and will be examined in the volume 92 in preparation [26]. The reason for this inclusion is the particular significance of this group of substances.

It is worthwhile noticing, as above mentioned, that some industrial sectors are excluded from the scope of Directive 67/548/EEC because they are covered by other EU legislations (*e.g.,* medicinal products for human or veterinary use, cosmetics, foodstuffs, animal feeding stuffs, pesticides, preparations containing radioactive substances). This approach implies the exclusion of important categories such as antitumoral drugs (to which medical personnel may be exposed), not taken into consideration by the EU Directive 67/548/EEC because belonging to the drugs sector, although they are recognised as human carcinogens by authoritative Agency like IARC, or listed in RoC or published by ISS expert [27].

It is therefore evident that the availability of evaluations performed by different institutions or agencies allows to fill the gaps due to the different selection rules adopted.

ORGANIZATION OF THE INFORMATION

For each entry included in the BDC, the information is standardized and structured in the following categories listed in *Table 4* and described as following:

Substance identification

For each substance the BDC gives the full chemical identification on the basis of internationally recognized nomenclature and identification codes, representing a search key.

The section includes:

- ***EC name:*** generally is the name of substances adopted in the Annex I to Directive 67/548 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 BDC IUPAC name is obtained from secondary sources;
- ***other international chemical name(s):*** (*e.g.,* ISO name) and synonyms (usual name, proprietary or trade names, abbreviation);
- ***CAS name:*** if available. It 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 BDC the CAS name is in English language and is obtained directly from the CAS Registry file (www.cas.org);
- ***Annex I name:*** is the name used for the substance in Annex I of Directive 67/548/EEC on classification, packaging and labelling of dangerous substances. Many substances appear in the Annex under different synonyms. It is obtained from the website 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);
- ***INCI name*** (International Nomenclature Cosmetic Ingredients)**:** from official INCI website (http://dg3.eudra.org/F3/inci/index.htm);
- ***definition for petroleum products:*** petroleum products are listed in EINECS with a name and definition that identifies each substance. The names and definitions are in accordance with CAS nomenclature, the established processing guidelines for petroleum substances, general petroleum chemistry, and literature of speciality product manufacturers. The definitions identify: starting materials (stream source); process; boiling range or other appropriate physical characteristics; carbon (alkyl) range; typical chemical composition;
- ***CAS number:*** if available, is an unique numerical identifier created and assigned by the Chemical Abstract Service 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 BDC, 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*, 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 tipe XXX-XXX-X. Information 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:*** if available. 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;
- ***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 online;
- ***ISS number:*** numeric code assigned by the National Inventory of Chemical Substances of Istituto Superiore di Sanità [28].

Hazard classification

This section includes the complete European Union Hazard Classification according to Directive 67/548/EEC. Search on Annex I of 67/548/EEC is obtained through the official website of the ECB http://ecb.jrc.it/classification-labelling/search-classlab/. The section is subdivided in:

- ***classification*** including hazard category(ies) and risk phrases. BDC also reports substances listed in Annex I to Directive 67/548/EEC for endpoints different than "carcinogenesis". However, the

institutions report the carcinogenicity classification, when appropriate. This is the case of styrene (CAS number 100-42-5 and BDC number 683) classified in Annex I to Directive 67/548/EEC as flammable, harmful by inhalation and irritating to eyes and skin (risk phrases R10, R20 and R36/38) in 1991 [29]. Moreover, in 1987, the IARC classified styrene in 2B (possible carcinogen to human) with inadequate evidence for carcinogenicity in humans and limited in experimental animal based on genotoxicity and metabolism to styrene oxide [13]. In 1994 styrene remained in 2B group but the classification was based on "limited" human data and "limited" animal data [30] and in 2002 the classification was reaffirmed and data descriptors changed in inadequate evidence in humans and limited evidence in animals [31]. Moreover, styrene has been nominated by Lorenzo Tomatis (former IARC director) for possible listing in the 12th edition of RoC based on 2002 IARC evaluation [32, 33];

- ***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) [34]. Generic limits may not reflect, in fact, the potency of a carcinogen in a preparation as such, but only a level of concern for the seriousness of health effects like carcinogenicity. In absence of specific limits, the general concentration limits reported in the preparation Directive (1999/45/EC) apply. They are 0.1% for category 1 and 2 carcinogens, and 1% for category 3 carcinogens. Specific limits are available only for few carcinogens (*e.g.* benzo(a)pyrene);
- ***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) [16].

Table 4 | *Structure of the BDC (Carcinogens Data Bank)*

Substance identification
Synonyms
CAS name
EC name
Annex I name
IUPAC name
IARC name
Other chemical names
Trade names
Colour Index generic names
INCI name
Definition for petroleum products
Identification Codes
CAS number
EC number
Index number
ISS number
CI number
Description of the family
Hazard classification according to Directive 67/548/EEC
Complete classification
Specific concentration limits in preparations
Adaptation to technical progress
Information on production volume within the European Market
Carcinogenesis evaluations
International Agency for Research on Cancer (IARC) Evaluation
Degree of evidence of carcinogenicity in humans
Degree of evidence of carcinogenicity in experimental animals
Overall evaluation
Bibliographic references
Link to IARC summary evaluation
US Environmental Protection Agency
Classification
Basis for classification
Guidelines for carcinogen risk assessment
Proposed guidelines for carcinogen risk assessment
Report on Carcinogens (RoC)
Classification
Link to substance profile
Italian National Toxicology Advisory Committee (CCTN)
Carcinogenic classification
Mutagenesis classification

Carcinogenesis evaluations

This section includes evaluations performed by different institutions. Moreover it consents the access to original documents (such as IARC *Summary Evaluation* and NTP *Substance Profile*) describing the rationale and method used to develop the classification, so facilitating the understanding of the classification.

International Agency for Research on Cancer

The section is structured as follow:

- ***degree of evidence for carcinogenicity in humans.*** This section includes the epidemiological evidence, characterized using the following standard descriptors of the levels of evidence: *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.*** This section includes the evidence in experimental animals, characterized using standard descriptors of levels of evidence: *sufficient evidence of carcinogenicity, limited evidence of carcinogenicity, inadequate evidence of carcinogenicity, evidence suggesting lack of carcinogenicity*;
- ***carcinogenesis category.*** This subsection includes the carcinogenic classification adopted by the IARC, based on the description of the epidemio-

logical 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)*;
- ***bibliographic reference.*** The most recent relevant IARC Monograph including the carcinogenesis category. All previous IARC Monographs are included;
- ***summary evaluation*** obtained through the official website of the IARC, containing summary of scientific data and evaluations developed by the IARC Working Group.

Report on Carcinogens

The section includes:
- ***carcinogenesis category*** adopted for substances or classes of chemicals classified as *known to be a human carcinogen, or reasonably anticipated to be a human carcinogen* according to 11th RoC;
- ***substance profiles*** obtained through the official website of the NTP, containing a brief description of each substance with a summary of the evidence for its carcinogenicity; relevant information on properties, use, production and exposure; and a summary of the regulations and guidelines that are likely to decrease the exposure to the substance. Each profile includes references to scientific literature used to support the listing.

Environmental Protection Agency

The section includes:
- ***carcinogenesis category*** established by the USEPA using its *Guidelines for carcinogen risk assessment* published for the first time in 1986 [5], revised in 1996 [6] and 1999 [7], and finally in 2005 [8]. BDC takes into consideration substances included in the database Integrated Risk Information System (IRIS) (www.epa.gov/iris/subst/) containing downloadable cancer health hazard information for approximately 540 substances [35]. Data are obtained via the EPA website. It is worthwhile noticing that IRIS, which contains EPA's scientific position, does not present regulatory standards *per se* but provides a basic information, available for regulatory purposes;
- as a consequence of the development of new *Guidelines for carcinogen risk assessment*, for several substances contained in IRIS, assessments can be found carried out with the 1986 available guidelines [5] but also in accordance to the 1996 proposed guideline [6] or under the review draft for 1996 [7] and/or the final 2005 guidelines [8]. Therefore, for the same substance, classification according respectively to the old and the new guidelines are available in the BDC (*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], EPA 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" [36].

National Toxicological Advisory Committee

Carcinogenesis category adopted by the National Toxicological Advisory Committee. The CCTN last evaluations were carried out in 2001 because it was no longer active after this date.

Indication of Production Volume in the European Union

In order to obtain an indication of the importance and the diffusion of interested substances, for each agent included the BCD reports its production volume within the European Community. Indications are obtained through EU ESIS (European chemical Substances Information System), an IT (Information Technology) system which gives access to information on chemicals on the European Chemicals Bureau's (ECB) website (http://ecb.jrc.it):
- ***HPVC substance*** (High Production Volume Chemicals), listed in the Annex I to the Regulation 93/793/EEC [37] on the evaluation of the risks of Existing Chemicals, which have been imported or produced within the European Community in quantities exceeding 1000 tonnes per year per manufacturer/importer. The current HPVC 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 LPVC list contains 7802 chemical substances.

The production volume of agents in EU has been checked and reported and it is indicated the lack of data on production volume.

UPDATING THE DATABASE

The BDC is in continuous evolution and is regularly updated taking into account both new EU legislations (new updatings of Annex I) and new published evaluations. In particular the database can be revised in the occurrence of:
- the publication of a new IARC Monograph. To date IARC has published authoritative monograph on hazard posed by more than 900 agents. Up to date (December, 2007) the IARC has published 88 monographs. Volume 89 is expected and other eight monographs are in preparation;
- the publication of the new ATP of Directive 67/548/EEC with consequent updating of Annex I in terms of updatings and new entries. At present the 29th ATP is in force and the 30th and 31st ones are at the

stage of "Final proposal of the Technical Committee Classification and Labelling", according to the ECB's website [38]. 30th ATP will insert twelve entries containing substances newly classified as carcinogenic category 2 and ten entries containing substances newly classified as carcinogenic category 3;
- the new *Reports on Carcinogens* by the DHHS. As an example, the 11th RoC was released on January 31, 2005. The 12th RoC is currently under review and its publication is foreseen for the end of 2007. 12th RoC will introduce several new additions [32, 33].

PROCEDURES FOR ACCESSING AND QUERYING THE BDB

Each agent can be searched in several ways:
- *simple:* through the query of single field or fragment of field as indicated in *Table 2* (*e.g.,* identification codes: CAS registry number, EC number, Index number if available; name or fragment of name etc.). The search with identification codes will produce an exact information. The BDC result is in Italian language but substances are searchable through all Italian and English synonyms. It is also possible to truncate with an asterisk (*), either in front of or after a fragment of name. In this case the search result gives less precise information;
- *advanced:* the previous search criteria can be combined using the logic operator AND;
- *by categories:* it is possible to make a search for specific categories of interest. This search allows to identify for instance substances classified in a specific group (*e.g.,* carcinogenic category 1 by EU; or mutagenicity category 2 by EU; or probable human carcinogen – based on limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals (Group B1) by USEPA or probably carcinogenic to humans (Group 2A) by IARC.

DEALING WITH CLASSIFICATION DIFFERENCES

As above mentioned, each institution follows a well established procedure according to specific classification schemes. The reasons for different classifications of the same chemical are various and can be explained with reference to:
- the documentation used; some institutions, such as IARC, base their classifications only on data published in the open literature, whereas other institutions, such as the European Union, review all available data, including unpublished data;
- the scope of different programs; for example, while many countries classify chemicals to estimate risks and set Occupational Exposure Limits, European Union classifies chemicals for labelling and establishing use restrictions purposes;
- different criteria in selection of substances for the assessment. There are sometimes significant differences in the selection procedure of agents to be considered. As mentioned, for instance antitumoral drugs are not taken into consideration by the EU Directive 67/548/EEC and by USEPA although they are recognised as human carcinogens by IARC or listed in RoC;
- differences in consideration of mechanisms, biotransformation, toxico-kinetics. For instance in 1991 IARC decided to introduce in making overall evaluations also data on mechanism if available [39]; *e.g.* a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or on the contrary available data demonstrate that the mechanism in experimental animals also operates in humans. Data on mechanisms have influenced the IARC classification of several substances modifying the overall evaluation in terms of an upgrading, when there is strong evidence that carcinogenesis in experimental animals is mediated by mechanisms that do operate in humans (this is the case of ethylene oxide) or downgrading, when there is strong and consistent evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans or is not predictive of carcinogenic risk to humans (this is the case of a relatively few well documented agents, *e.g.,* d-limonene, saccharin and its salts, melamine downgrading from Group 2B to Group 3 on the basis of such evidence);
- the date of the classification or its update can also influence the classification. Additional data may become available after the classification. This is the case of styrene classified by EU in 1991 [29] and re-evaluated by IARC more than ten years later [31].

As a result an agency may classify the same agent as human carcinogen while another institution does not. Moreover some agencies carry out only qualitative evaluations while other provide quantitative assessment (as IRIS). Nevertheless, in conclusion, there are no dramatic differences between the various existing classifications.

FUTURE PERSPECTIVES

In the future the Classification and Labelling system, as described in Directive 67/548/EEC and updated by Directive 2001/59/EC, will be substituted by a Global Harmonized System (GHS), agreed at UN level, with the aim of having a unique classification system all around the world. The GHS is about to be implemented in the EU through a regulation which will repeal the present EU legislation (Directive 67/548/EEC and Directive 1999/45/EEC).

The GHS criteria for carcinogens foresee 2 categories (more details in *Table 5*) [40]:
- category 1 *(known or presumed human carcinogens)* subdivided into category 1A *(known to have carcinogenic potential for humans*; the placing of a chemical in such category is largely based on human evidence)

Table 5 | *Criteria for carcinogens*

	European Union	
Category 1 T; R45 T; R 49	*Substances known to be carcinogenic to man*	Sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.
Category 2 T; R45 T; R 49	*Substances which should be regarded as if they are carcinogenic to man*	There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of: - appropriate long-term animal studies, - other relevant information.
Category 3 Xn; R 40	*Substances which cause concern for man owing to possible carcinogenic effects*	Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in category 2.
	Global Harmonized System	
Category 1A	*Chemicals known to have carcinogenic potential for humans; the placing of a chemical is largely based on human evidence*	
Category 1B	*Chemicals presumed to have carcinogenic potential for humans; the placing of a chemical is largely based on animal evidence*	Based on strength of evidence together with additional considerations, such evidence may be derived from human studies that establish a causal relationship between human exposure to a chemical and the development of cancer (known human carcinogen). Alternatively, evidence may be derived from animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case by case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.
Category 2	*Suspected human carcinogens*	The placing of a chemical in category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the chemical in Category 1. Based on strength of evidence together with additional considerations, such evidence may be from either limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

and 1B (*presumed to have carcinogenic* potential for humans; the placing of a chemical in such category is largely based on animal evidence) and
- category 2 *(suspected human carcinogens)*.

The only difference in the two subcategories 1A and 1B is that the source of evidence is different, whilst the strength of the evidence can be considered to be the same in both cases.

The classification criteria for the three categories, 1A, 1B and 2, are broadly similar to those for category 1, category 2 and category 3 carcinogens in the current EU system.

The classification is based on *strength of evidence* (the Guidelines refer to the terms *"sufficient"* and *"limited"* as used by IARC) and *additional considerations (weight of evidence)*.

Classification as a carcinogen is made on the basis of evidence from reliable and acceptable methods, and is intended to be used for chemicals which have an intrinsic capacity to produce such toxic effects. The evaluations should be based on all existing data, peer-reviewed published studies and additional data accepted by regulatory agencies.

A mixture will be classified as a carcinogen when at least one ingredient has been classified as a category 1 or category 2 carcinogen and is present at or above the following appropriate cut-off value/concentration limits [40]:
- *category 1 carcinogen:* ≥ 0.1 %;
- *category 2 carcinogen:* ≥ 1.0%. If a category 2 carcinogen ingredient is present in the mixture at a concentration of ≥ 1%, both an SDS and a label would generally be expected.

BDC intends to provide an easy tool for experts, researchers and risk managers dealing with carcinogenic agents.

All available classifications and evaluations are presented without ascribing any priority. Each of them should be considered within the time period of its publication and in the context of scientific evidence and of classification rules existing at that period.

Under the GHS regulation [40], once adopted, the substances will mostly be self-classified by industry, apart the CMR and respiratory sensitizers for which a harmonised classification will continue to be produced by a group of experts at community level.

CONCLUSIONS

The consideration of different information sources and of different evaluations of expert groups and different institutions is certainly appropriate to this complex and continuously evolving topic. Furthermore, we consider useful to have an extended and detailed view of the carcinogenic agents, independently of their relevance as environmental contaminants, row

materials, intermediate or final industrial products, medicine drugs, intentionally produced hazardous chemicals like pesticides, or agents present in some industrial exposures.

Exposure may occur for the general population (adults, females and males, children, elderly, disease affected people) and workers. For instance the risk associable to a carcinogenic drug, like certain antiblastic agents, may affect the workers producing them, the medicinal personnel employed in patient treatment, and also the treated patients for a secondary effect.

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