

# The ISS Sensitizing Agents Data Bank (BDS)

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**Summary.** The Istituto Superiore Sanità has developed a data bank on sensitizing substances (*Banca Dati Sensibilizzanti*, BDS), available on website ([www.iss.it/bdse/](http://www.iss.it/bdse/)), sharing complete, controlled and updated information coming from different sources, such as scientific publications, international agencies and governmental or non governmental organizations. It is worthwhile that the main objective of the BDS is not the classification of sensitizing or potentially sensitizing agents within specific risk classes, but it is essentially to provide concise and non confidential information related to this endpoint. At present, the BDS includes: all the substances officially classified by European Union, (Annex I to Directive 67/548/EEC), some substances listed in Annex I (Directive 67/548/EEC) for endpoints different than "sensitization" but indicated as sensitizers by other relevant institutions, all the substances indicated as sensitizers by relevant agencies or institutions (ACGIH, DFG), some substances indicated as sensitizers by industry and other non-governmental organizations (ETAD and HERA), all the substances regarded as "potentially sensitizing dyes" by the Commission of the European Community for the award of the Community eco-label to textile products, some substances for which, even in the absence of any categorization by European Union, ACGIH or DFG, it is not possible to exclude a sensitizing potential on the basis of reliable documents.

*Key words:* database, sensitizers, allergic contact dermatitis, asthma, classification criteria, occupational diseases, hazardous substances.

**Riassunto** (*La Banca Dati Sensibilizzanti, BDS*). La banca dati su sostanze chimiche potenzialmente sensibilizzanti (Banca Dati Sensibilizzanti, BDS), predisposta e aggiornata dall'Istituto Superiore di Sanità, include tutte le sostanze classificate come sensibilizzanti dalla Unione Europea (nell'ambito della Direttiva 67/548/CEE), quelle classificate come tali da enti con competenza di valutazione del rischio per l'ambiente di lavoro (es. ACGIH e DFG) o anche in generale sostanze esaminate da istituzioni sia governative (US NTP) che di settore o industriali (ETAD, HERA). La BDS non si propone di classificare sostanze sensibilizzanti o potenzialmente tali, ma rende disponibili informazioni non riservate relative a questo endpoint. Le informazioni, presentate in forma sintetica, corredate da riferimenti bibliografici consentono di risalire alla fonte originale e in alcuni casi di collegarsi direttamente ad essa mediante la rete.

*Parole chiave:* basi di dati, sensibilizzanti, dermatite allergica da contatto, asma, criteri di classificazione, malattie professionali, sostanze pericolose.

## INTRODUCTION

### *Allergic diseases*

Adaptive immunity plays the important function of host defence against microbial infections, but immune responses are also capable of causing tissue injury and disease. Hypersensitivity diseases are caused by immune responses [1]. This term derives from the clinical definition of immunity as "sensitivity", which is based on the observation that an individual who has been exposed to an antigen exhibits a detectable reaction, or is "sensitive", to subsequent contacts with that antigen, the so-called

allergen. Hypersensitivity diseases are commonly classified according to the type of immune response and the effector mechanism responsible for cell and tissue injury (*Table 1*). This classification is useful because distinct types of pathogenic immune responses show different patterns of tissue injury and may vary in their tissue specificity. However, immunological diseases are often complex from the clinical standpoint, due to combinations of humoral and cell-mediated immune responses and multiple effector mechanisms.

Around the world allergies are one of the biggest health problems. They impair the quality of life of a large part of the population and have major economic repercussions. The symptoms of allergy are numerous and varied, ranging from a mild irritant to a severely debilitating chronic condition. They can be classified according to the organs or systems involved (respiratory tract, skin, gastrointestinal systems) and may include oculorhinitis, wheezing, asthma, urticaria, oral syndrome, upset stomach, diarrhoea, up to the generalized anaphylactic shock. Symptoms may be triggered by a wide number of causes: a reaction to food or food additives, to inhalant allergenic sources and/or pollutants in the air outside or at home, to chemicals in surroundings where we live or work or in everyday items we use. In susceptible individuals some substances cause skin sensitization (allergic contact dermatitis) and/or sensitization of the respiratory tract (allergic asthma and/or rhinitis). Contact allergies are generally manifested as contact eczema, the pathogenesis of which involves a T lymphocyte-mediated immune reaction of delayed type. Contact eczema is almost always caused by reactive substances of low molecular weight. Most of respiratory allergens are macromolecules, mainly proteins. The allergic reactions of the airways mostly involve reaction of the allergen with specific IgE antibodies and belong to the immediate hypersensitivity that can also cause systemic reactions and even anaphylactic shock. Low molecular weight substances can also induce specific immunological reactions in the airways. Some of these respiratory allergens are also contact allergens. The development of these diseases is determined by several factors, including, the potential sensitization resulting from the chemical properties of the substance, also the exposure concentration and the duration and way of exposure and the genetic predisposition of the subject.

The potential sensitization of a substance is not the same as the incidence of sensitizations which it causes, because the clinical significance of an allergen is not only determined by its sensitization potential, but also by the distribution of the substance and the possibilities of exposure to it. Besides, it is still not possible to determine generally applicable threshold concentrations either for the induction of an allergy (sensitization) or for triggering the allergic reaction in an already sensitized person.

### **Occupational allergy**

Allergic diseases represent important occupational health problems. In fact, it is estimated that 5% of isocyanate workers, 10-45% of proteolytic enzymes workers and 5-30% of cereals and flour workers develop symptoms of occupational asthma [2].

Occupational allergy represents a particular type of allergic disease: it can involve airways (occupational rhinitis and asthma) or skin (occupational dermatitis). Occupational rhinitis may precede occupational asthma (work related sneezing, nasal discharge and obstruction should alert to possible occupational disease). Occupational asthma is caused by sensitization to an agent inhaled in the workplace and usually presents with cough, wheezing and variable shortness of breath. Symptom onset is slow and may occur after years of repeated exposure to chemicals and allergens in the work environment. Occupational dermatitis is the most common cause of occupational disease. Substances in products that come into contact with the skin play an important role as exogenous factors in the triggering of allergic contact eczemas (type IV allergies) at home but also at work. A lot of common objects hold allergens which can cause allergic contact dermatitis: jewellery, cosmetics, drugs, shoes, textile, etc.

These products are dangerous both for workers and consumers: workers use daily these potentially sensitizing agents in workplaces, and the consumers use the finished products such as cosmetics, clothes, detergents etc.

### **The socio-economic impact**

It is worthwhile noticing that the study of allergenic substances is an important priority in European Union. The socio-economic costs of allergies for Europe are estimated in 1999 at € 29 billion/year. Chemical substances are considered to play a major role in inducing allergies either directly or by increasing susceptibility to natural allergens (e.g., pollen) [3]. Moreover a survey conducted in 2004 by the World Allergy Organization Specialty and Training Council estimated that 22% of the populations surveyed in 33 countries, representing a population of 1.39 billion people, may suffer from some form of allergic disease. The prevalence rates for allergy in the countries where physicians responded to the survey ranged from 7.5 (in Colombia) to 40% (in Japan

**Table 1** | Classification of immunological diseases

Type of hypersensitivity	Pathologic immune mechanisms
Type I: immediate hypersensitivity	IgE antibody
Type II: antibody mediated	IgM, IgG antibodies against cell surface or extracellular matrix antigens
Type III: immune complex mediated	Immune-complexes of circulating antigens and IgM or IgG antibodies
Type IV: T cell mediated	CD4+ T cells (delayed-type hypersensitivity) CD8+ T cells (T cell-mediated cytotoxicity)

and Ukraine) suggesting a mean of 22%. Italy, with about 10%, was between countries reporting the lowest rates [4].

### OBJECTIVE

The aim of the project was to develop a Data Bank on Sensitizing substances (BDS) available on the Istituto Superiore Sanità (ISS) website ([www.iss.it/bdse/](http://www.iss.it/bdse/)) sharing complete, controlled and updated information coming from different sources, such as scientific publications, international agencies and governmental or non governmental organizations.

The ISS producing the BDS to facilitate the access to updated and complete information on substances classified as sensitizing by European Union and other national or international institutions, or suggested by relevant scientific data as making part of this category. The experience acquired during the study of the allergic diseases by the working group of the ISS Section of Immune-mediated Diseases played a pivotal role in the realization of the project of BDS. Moreover, the experience gained in the realization of the data bank on carcinogenic agents (BDC), prepared and maintained by the ISS Section of Dangerous Substances and Preparations was of main help for the definition of the BDS structure [5]. Lastly, the realization of the project "Constitution of a data bank of substances present in the manufacturing process and in the end-product of the textile compartment" [6] recently completed, has provided important experience in the BDS field.

It is worthwhile underlining that the main objective of the BDS is not the classification of sensitizing or potentially sensitizing agents within specific risk classes, but it is essentially aimed to provide concise and non confidential information related to this endpoint. The consultation of the BDS allows access to the information produced by different national and international regulatory organizations, offering a wide view of the problem and a presumably useful support to the users. However, it must be underlined that the criteria for classifying chemicals adopted by different regulatory bodies are not harmonized among the various countries and institutions. Differences in the schemes for the classification cause variation in the designation of chemicals as sensitizers. These differences may have important implications for a wide number of activities linked to the management of the risk, including the definition of the limits for occupational exposure. On the other hand, experimental data acquired from scientific publications are not always in agreement, in particular when data obtained from studies on human subjects or laboratory animals are compared.

For example the designation of substance as a sensitizer by American Conference of Governmental Industrial Hygienists (ACGIH) is based on human or animal data [7]. Also the European Union nor-

mally uses evidence in humans and appropriate data from animal tests to classify as sensitizing [8], while the Deutsche Forschungsgemeinschaft (DFG) uses mainly human evidence and animal data in the case of limited availability of human data [9]. In addition the EU gives special relevance to chemical structure. For instance this is the case of isocyanates, automatically classified as sensitizers by inhalation unless there is evidence that the specific isocyanate does not cause respiratory hypersensitivity [8].

Moreover, differences in the classification may be due to different approaches for the definition of the groups of chemicals pertaining to the same classes. This is for instance the case of the group entry *chromium VI compounds* classified as skin sensitizing in Annex I of Directive 67/548/EEC. According to Directive 67/548/EE in the cases of the group entry the classification and labelling requirements will apply to all substances placed on the market, in so far as they are listed in EINECS (European Inventory of Existing Commercial Chemical Substances). Therefore, in the case of chromium VI compounds, the EU classification covers more than fifty chromium VI compounds listed in EINECS. ACGIH considers water soluble chromium VI compounds (*e.g.*, chromic acid, its anhydride, and the monochromates and dichromates of sodium, potassium, ammonium, lithium, cesium and rubidium) and insoluble Cr VI (*e.g.*, zinc chromate, calcium chromate, lead chromate, barium chromate, strontium chromate, and sintered chromium trioxide) giving different TLV values but without recommend SEN notation, while DFG considers as skin sensitizer chromium VI compounds (inhalation fraction), with the exception of those practically insoluble in water.

Therefore, one of the various reasons of this data bank production has been the need of preparing, as far as possible, a summary of the whole set of information available for the considered substances even if they do coincide, allowing an extended vision particularly in the case of absence of EU classifications and of differences among the various organizations.

However, it is important to stress that the BDS deals with effects that must be always regarded as potential, and the link between available data and probability that the substance is actually a sensitizing one is modulated by a number of factors, some of which are related to the complex aetiology of the allergic disease.

### SELECTION CRITERIA TO ADD A GIVEN SUBSTANCE IN THE DATABASE

At present, the BDS contains over 700 records, each concerning agents which have been identified and considered by national or international Agencies dealing with the identification and classification of the health risks, including the evaluation of the sensitizing potential. *Table 2* presents a selection of national and international organizations used as sources for the BDS. The term "agent", ac-

**Table 2** | *Some of the national and international agencies and organizations used as sources for BDS*

Organization	Mission
<b>ACGIH</b> American Conference of Governmental Industrial Hygienists <a href="http://www.acgih.org">www.acgih.org</a>	ACGIH is a non-governmental agency that publishes yearly recommended occupational health limits called threshold limit values (TLV)
<b>BIBRA INTERNATIONAL</b> Formerly BIBRA Toxicology International <a href="http://www.bibra.co.uk">www.bibra.co.uk</a>	The BIBRA toxicity profiles are critical reviews of the most pertinent toxicological data published on commercially important chemicals prepared by experienced toxicologists
<b>BUA Report</b> Advisory Committee on Existing Chemicals of Environmental Relevance <a href="http://www.hirzel.de/bua-report/download.html">http://www.hirzel.de/bua-report/download.html</a>	The Advisory Committee on Existing Chemicals of Environmental Relevance (BUA) was established to help the German federal government in the field of existing chemicals. In an agreement between federal government, scientific community, and the chemical industry, it was associated with the German Chemical Society (GDCh, Gesellschaft Deutscher Chemiker) to ensure objective work, carried out in accordance with scientific principles. The BUA also selects and assesses existing chemicals with a lower production volume in the range of 100-1000 tons/year. Comprehensive reports are published on chemicals suspected of having a hazardous potential
<b>DFG</b> Deutsche Forschungsgemeinschaft <a href="http://www.dfg.de/en/">http://www.dfg.de/en/</a>	The Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) is the central, self-governing research organization that promotes research at universities and other publicly financed research institutions in Germany. Through its commissions, the DFG provides scientific advice for politics and administration. The experts of DFG-Senate Commission on the Investigation of Health Hazards of Chemical Compounds in the Work Area each year compile the List of MAK and BAT Values (maximum concentration at the workplace) to reflect the latest scientific knowledge in occupational health and safety
<b>ETAD</b> Ecological and Toxicological Association of Dyes and Organic Pigments Manufacturers <a href="http://www.etad.com">www.etad.com</a>	ETAD formed to represent the interests of the organic colorant industries on matters relating to health and environment is an international organization. ETAD seeks to base its positions on sound science and to co-ordinate the efforts of its members to minimize any possible adverse impact of organic colorants on health and environment. Member companies are obliged to adhere to the ETAD Code of Ethics, which is based on the principles of responsible care
<b>HAZ-MAP</b> Hazardous substances data bank <a href="http://hazmap.nlm.nih.gov">http://hazmap.nlm.nih.gov</a>	Available on the National Library of Medicine's TOXNET system is an occupational health database designed for health and safety professionals and for consumers seeking information about the health effects of exposure to chemicals and biologicals at work. Haz-Map links jobs and hazardous tasks with occupational diseases and their symptoms
<b>HERA</b> Human and Environmental Risk Assessment <a href="http://www.heraproject.com">www.heraproject.com</a>	HERA project is a voluntary Industry program to carry out human and environmental risk assessment of chemicals used in household detergent and cleaning products between CEFIC, the Council of the European Chemical Industry and AISE, the European Soap and Detergent Industry
<b>ICSC</b> International Chemical Safety Cards <a href="http://www.cdc.gov/niosh/ipcs/nicstart.html">http://www.cdc.gov/niosh/ipcs/nicstart.html</a>	The International Chemical Safety Card (ICSC) project is an undertaking of the International Programme on Chemical Safety (IPCS), developed in the context of the cooperation between the IPCS and the Commission of the European Communities. The IPCS is a joint activity of three cooperating international organizations: namely the United Nations Environment Programme (UNEP), the International Labour Office (ILO), and the World Health Organization (WHO) with the main objective to carry out and disseminate evaluations of the hazards posed by chemicals to human health and the environment
<b>NTP</b> National toxicology program <a href="http://ntp.niehs.nih.gov/">http://ntp.niehs.nih.gov/</a>	The NTP is an interagency program with the mission to coordinate, conduct and communicate toxicological research across the US Government. NTP maintains an objective, science-based approach in dealing with critical issues in toxicology and is committed to use the best science available to prioritize, design, conduct, and interpret its studies. The NTP maintains a balanced research and testing program that provides data addressing a wide variety of issues important to public health. The NTP, which can be accessed from the website, actively seeks to identify and select for study chemicals and other substances for which sufficient information is not available to adequately evaluate potential human health hazards
<b>SCCP</b> Scientific Committee on Consumer Products <a href="http://ec.europa.eu/health/ph_risk/committees/04_sccp/04_sccp_en.htm">http://ec.europa.eu/health/ph_risk/committees/04_sccp/04_sccp_en.htm</a>	Independent non-food Scientific Committees of the European Commission established to answer to questions concerning the safety of consumer products (non-food products intended for the consumer). In particular, the Committee addresses questions related to the safety and allergenic properties of cosmetic products and ingredients with respect to their impact on consumer health, toys, textiles, clothing, personal care products, domestic products such as detergents and consumer services such as tattooing

ording to the International Agency for Research on Cancer (IARC) definition [10], includes specific chemicals (dyes, chemical intermediates, pesticides, drugs, food additives) as well as groups of related chemicals, complex mixtures, biological organisms, plant or animal proteins, fragrances, working and environmental exposures during manufacturing processes, cultural or behavioural practices.

The BDS includes the following classes of substances:

**1) All the substances officially classified by European Union, listed in Annex I to Directive 67/548/EEC** as respiratory sensitizer with the symbol “Xn” (harmful) and the *risk phrase R42* (may cause sensitization by inhalation) or as skin sensitizer with the symbol “Xi” (irritant) and *risk phrase R43* (may cause sensitization by skin contact) or with symbol “Xn” and combined risk phrase R 42/43 (may cause sensitization by inhalation and skin contact). At present, Annex I of the Directive 67/548/EEC lists 27 respiratory sensitizers, 677 skin sensitizers and 72 respiratory/skin sensitizers [11];

**2) Selected substances listed in Annex I to Directive 67/548/EEC for endpoints different than “sensitization” but indicated as sensitizers by other relevant institutions.** Generally, this is the case of substances with rather old classification (issued beginning of ‘90) that has not taken into account sensitization and for which at present new pertinent scientific studies and evaluations by national or international institutions, published after the issue of European Union classification, indicate sensitizing power.

*Examples*

2-Methylpentane-2,4-diol (CAS number 107-41-5 and BDS number 2999), high production volume chemical [12] used in cosmetics and hydraulic brake fluids:

- classified in Annex I to Directive 67/548/EEC as irritating to eyes and skin (risk phrase R36/38), in 1991 [13];
- recognized to be responsible of allergic contact dermatitis and of occupational asthma from the HAZ-MAP (occupational toxicology database of chemicals designed to link jobs to hazardous job tasks which are linked to occupational diseases and their symptoms produced by the National Library of Medicine available on <http://hazmap.nlm.nih.gov/>) [14];
- for which the International Chemical Safety Cards (ICSC Card) points out that *repeated or prolonged contact with skin may cause dermatitis* [15] and
- open literature reports that on *delayed contact allergic reactions may occur*.

Diethanolamine (CAS number 111-42-2 and BDS number 565) an high production volume chemical used as a detergent in paints, metalworking fluids, shampoos, and other cleaners:

- classified by the European Union as harmful if swallowed (R22), irritating to skin (R38), risk of serious damage to eyes (R41) and harmful: dan-

ger of serious damage to health by prolonged exposure if swallowed (R48/22) in 1998 [16];

- designated in the List of MAK and BAT values as a *skin-sensitizer* with “Sh” by the Deutsche Forschungsgemeinschaft (DFG) [9] and
- for which at present, the ICSC Card points out that *repeated or prolonged contact may cause skin sensitization* [15];

**3) All the substances not officially classified by the EU which, according to lists of occupational exposure limits by relevant agencies or institutions have been indicated to be sensitizing.** Make part of this group substances designated as sensitizers by:

- American Conference of Governmental Industrial Hygienists (ACGIH) with “SEN” notation [7] or by
- Deutsche Forschungsgemeinschaft (DFG) in the list of MAK and BAT values as *skin-sensitizing substances* with “Sh”, *substances causing airway sensitization* with “Sa” or as *skin/airway-sensitizing substance* with “Sah” [9].

At present DFG designates 238 agents as sensitizers, of which respectively 15 as airway sensitizers, 185 as skin sensitizers and 38 as airway and skin sensitizers while, ACGIH lists 28 substances as sensitizers. At present the BDS includes all the substances designated as sensitizer by the ACGIH and those taken into consideration by the DFG (to be completed).

*Example*

1,4-Diamino-2-nitrobenzene (CAS number 5307-14-2 and BDS number 1637) used as semipermanent and permanent hair dyes:

- not officially classified by the European Union;
- for which numerous scientific publications, available in open literature, report sensitization effects on human subjects;
- for which ICSC Card points out that *contact repeated or prolonged can cause cutaneous sensitization* [15];
- designated by the DFG as skin-sensitizing substance with “Sh” notation because *causes allergic reactions on the skin relatively frequently in person sensitized to arylamines and, in particular, sensitizing effect have also been detected in animal experiments* [17];
- regarded as responsible of allergic contact dermatitis according to the information provided by the HAZ-MAP database [14];

**4) Substances not officially classified by the EU according to the Directive 67/548/CEE but taken into account for skin sensitization as a toxicity endpoint by industry and other non-governmental organizations such as:**

- the Ecological and Toxicological Association of Dyes and Organic Pigments Manufacturers (ETAD), an international association aimed to represent the interests of the organic colorant industries on health effects and environment im-

pect topics [18] particularly involved in skin sensitization risk from dyed textiles or

- the Human and Environmental Risk Assessment (HERA), an European voluntary project launched in 1999 by the Association Internationale de la Savonnerie, de la Détergence et des Produits d'Entretien (AISE, International Association for Soaps, Detergents and Maintenance Products) representing the formulators and manufacturers of household cleaning products and the European Chemical Industry Council (CEFIC, Council Européenne de l'Industrie Chimique) representing the suppliers and manufacturers of the raw materials, to carry out Human and Environmental Risk Assessment on ingredients of household cleaning products [19].

This is the case of a remarkable number of reactive dyes, for which there is evidence that they have caused respiratory sensitization in workers occupationally exposed. For these dyes, ETAD's assessment fulfils the criteria for hazard classification of respiratory and/or skin sensitizers, which therefore should carry the label Xn (harmful) R42 (may cause sensitization by inhalation) or Xi (irritant) R43 (may cause sensitization by skin contact) or the combined risk phrase R42/43 to reflect their sensitization potential [18].

#### Examples

1-Propanaminium, 3-amino-N-(carboxymethyl)-N, N-dimethyl-, N-cocoacyl derivatives, inner salts (CAS number 61789-40-0 with BDS number 2823) a high production volume chemical amphoteric surfactant:

- not officially classified by the European Union;
- regarded as sensitizing by open available scientific literature;
- for which risk assessment carried out by the HERA gives extensive data on contact allergy related to the substance [19].

Similar is the case of CI Reactive Black 5 (CAS number 17095-24-8 and BDS number 2711) a textile diazo dyestuff:

- not officially classified by the European Union;
- classifiable as sensitizing by contact with the skin and by inhalation (risk phrase R42/43) by the ETAD [18];
- for which extensive data, available in open scientific literature, describe sensitization on human subjects [20].

It should be noted that, in several cases, substances which have not been classified yet according to Annex VI of the Directive 67/548/EEC [8] are often already self-classified by the responsible for their marketing.

At present the BDS includes all the substances considered classifiable as sensitizing by the ETAD, and some of those taken into consideration by the HERA;

**5) All the substances regarded as potentially sensitizing dyes by the Commission of the European Community for**

**the award of the Community eco-label to textile products** [21].

The potentially sensitizing dyes identified by European Commission, all belonging to the class of disperse dyes, are included in the BDS;

**6) Selected substances for which, even in the absence of any categorization by European Union, ACGIH or DFG, it is not possible to exclude a sensitizing potential on the basis of reliable documents, such as those published by:**

- the International Programme on Chemical Safety (IPCS) a joint activity of United Nations Environment Programme (UNEP), International Labour Organization (ILO) and World Health Organization (WHO) that carry out and disseminate evaluations on hazards posed by chemicals to human health and to the environment [15];
- the British Industrial Biological Research Association (BIBRA), an international Ltd that produce Toxicity Profiles, that are critical reviews of the most pertinent toxicological data published on commercially important chemicals with particular emphasis to sensitizing data [22];
- the Scientific Committee on Cosmetic Products (SCCP) of the European Commission, particularly addressed toward questions concerning the safety and the allergenic properties of cosmetic products and ingredients with respect to their impact on consumer health, toys, textiles, clothing, personal care products, domestic products such as detergents and consumer services such as tattooing [23];
- the GDCh (Gesellschaft Deutscher Chemiker) Advisory Committee on Existing Chemicals (abbreviation BUA) that has produced comprehensive reports (BUA Report) on about 300 chemicals suspected of having a hazardous potentials. BUA Reports serve the German federal government as a basis for measures to regulate environmental and health hazards [24].

#### Example

Propylene glycol (CAS number 57-55-6 and BDS number 2434), high production chemical used as antifreeze, emulsifier and solvent:

- neither officially classified by the EU, nor considered by ACGIH or by DFG;
- for which articles available in the literature and published reports [24], suggest a potential sensitizing property;
- IPCS points out that *repeated or prolonged contact with this substance can cause sensitization of the skin* [15] and
- BIBRA points out that *is able to induce reactions of cutaneous sensitization in some individuals* [22].

## ORGANIZATION OF THE INFORMATION

Data provided for each substance are organized into different fields. Each entry contains data structured in the following broad categories listed in Table 3.

**Table 3** | Structure of the BDS

<p><b>Substance identification</b></p> <p><i>Synonyms</i></p> <ul style="list-style-type: none"> <li>- CAS name</li> <li>- EC name</li> <li>- IUPAC name</li> <li>- Other chemical names</li> <li>- Trade names</li> <li>- Colour Index Generic names</li> <li>- INCI name</li> </ul> <p><i>Identifiers</i></p> <ul style="list-style-type: none"> <li>- CAS number</li> <li>- EC number</li> <li>- Index number</li> <li>- CI number</li> </ul>
<p><b>Hazard Classification according to Directive 67/548/EEC</b></p> <ul style="list-style-type: none"> <li>- Complete classification</li> <li>- Specific concentration limits in preparations</li> <li>- Adaptation to Technical Progress</li> </ul>
<p><b>Sensitizing potential</b></p> <p>Standard sentence</p> <p>Note to the standard sentence.</p> <p>Human or animal models.</p> <p>Relevant references:</p> <ul style="list-style-type: none"> <li>- authors</li> <li>- title</li> <li>- source</li> <li>- type of publication</li> <li>- source of data</li> <li>- abstract/summary</li> <li>- reference web</li> </ul>
<p><b>Carcinogenesis Evaluations</b></p> <ul style="list-style-type: none"> <li>- International Agency for Research on Cancer (IARC) evaluation</li> <li>- US Environmental Protection Agency Classification</li> <li>- Report on Carcinogens (RoC) Classification</li> </ul>
<p><b>Occupational Exposure Limits</b></p> <ul style="list-style-type: none"> <li>- American Conference of Industrial Hygienists (ACGIH) threshold limit values</li> <li>- Commission of the Deutsche Forschungsgemeinschaft (DFG) sensitization notation</li> </ul>

### Substance identification

It is often quite difficult to determine the exact chemical identity; this in particular for the case of dyes so that numerous and different information sources are necessary to this purpose. In general, no single resource exists that provide all the information necessary for a complete knowledge of both the identification and the intrinsic properties of a substance [25]. A number of different resources is currently available each of which refers to specific areas (identification, toxicology, risk assessment) and each of them with some advantages but also some limitations. In the BDS all data concerning substances identification come from primary sources, mainly chemical dictionaries, such as Chemical Abstracts Registry File or ChemID (Chemical Identification from the US National Library of Medicine) or catalogues such as Colour Index and qualified network such as ESIS (European Substances Information

System) available on the official website of the European Chemicals Bureau.

In the BDS substance identification is on the basis of Synonyms and Identifiers. For all substance names and synonyms are listed. Synonyms include International Union of Pure and Applied Chemistry name (IUPAC), EC name, CAS name, other chemical names, trade names, common or general names, other internationally recognized nomenclature such as Colour Index Generic Names or INCI name (International Nomenclature Cosmetic Ingredients).

Identification is completed by internationally recognized identifiers that are codes such as:

- CAS number, assigned by the chemical abstracts service of the American Chemical Society, uniquely identifies a specific chemical compound and eliminates ambiguity in identification;
- EC number, corresponding to EINECS number for European Inventory of Existing Chemical Substances or ELINCS number for European List of Notified Chemical Substances;
- Index number, identification code given to the substance officially classified as dangerous in Annex I of Directive 67/548/EEC;
- Colour Index Constitution Number which gives colouristic classification.

### Evaluation of the sensitizing potential

This section is structured in the following subcategories:

**Standard sentences.** Since BDS is a factual database aiming at immediately providing useful information in simple form and, possibly, complete, for providing a conclusive evaluation for every substance, some standard sentences have been defined in order to summarize the overall assessment of the potential sensitizing properties. The standard sentences and the different criteria of sentence assignment substances under evaluation are summarized in *Table 4*.

**Note to the standard sentences.** Sometimes, when ever considered appropriate, the standard sentence is clarified by an explanatory note.

**Human or animal models.** It is reported if the data (both positive and negative obviously for the sensitization) are obtained by observations on human subjects or animals or both.

**Relevant references.** For each substance, a list of the relevant and remarkable bibliography is added. The abstracts from the original publication or an *ad hoc* predisposed summary is given when available. For each reference the following data are reported if available:

- authors;
- title;
- complete bibliographical reference;
- type of publication (original article, monograph, technical report, case report, review);
- source of data: for each reference, the origin of the information is reported (e.g., PubMed, TOXLINE, BIBRA, ETAD, HERA, IPCS, ACGIH);
- abstract/summary (if available);
- reference website (if available).

Information concerning sensitizing potential is selected from:

- factual databases that provide detailed and peer reviewed data such as HSDB (Hazardous Substances data bank);
- bibliographic databases such as PubMed and TOXLINE; the MeSH (Medical Subject Headings) descriptors “sensitization, dermatitis, allergy” as well as “hypersensitivity” were used to search primary literature;
- books, government documents, technical reports;
- web: there are now many good quality websites of producing companies covering the field of toxicology, that can be useful in the case of absence of data in the above listed sources, to retrieve relevant data.

Generally, relevant publications were retrieved using CAS registry number or chemical names. In the case of dyes, CI (colour index) names and numbers were used.

**Table 4** | Standard sentences and the different criterions of sentence assignment to the given substances under evaluation

Standard sentences	Criteria of sentence assignment
Substance classified by EU according to Directive 67/548/EEC as respiratory sensitizer with the risk phrase R42	This group includes all substances officially classified by EU, listed in Annex I to Directive 67/548/EEC as sensitizer.
Substance officially classified by EU according to Directive 67/548/EEC as skin sensitizer with the risk phrase R43	
Substance officially classified by EU according to Directive 67/548/EEC both as respiratory sensitizer and as skin sensitizer with the combined risk phrase R42/43	
Substance officially classified by EU according to Directive 67/548/EEC both as respiratory sensitizer and as skin sensitizer with the combined risk phrase R42/43, it has not been published, yet	This group includes all the substances officially classified by EU, listed in Annex I to Directive 67/548/EEC as sensitizer.
Substance officially classified by EU according to Directive 67/548/EEC for endpoints different than “sensitization”	Some of the substances listed in Annex I to Directive 67/548/EEC for endpoints different than “sensitization” but indicated as sensitizers by other relevant institutions, are listed in this group. Generally, this is the case of substances with rather old classification (issued beginning of ‘90) that has not taken into account sensitization, and for which at present new pertinent scientific studies and evaluations by national or international institutions, published after the issue of EU classification, indicate sensitizing power.
Substance classified as sensitizer by other relevant agencies or institutions (not EU)	This group include all substances not officially classified by the EU which, according to lists of occupational exposure limits by relevant Agencies or Institutions have been indicated to be sensitizing. In this group are listed substances designated as sensitizers by: - American Conference of Governmental Industrial Hygienists (ACGIH) with “SEN” notation or - Deutsche Forschungsgemeinschaft (DFG) in the List of MAK and BAT Values as <i>skin-sensitizing substances</i> with “Sh”, <i>substances causing airway sensitization</i> with “Sa” or as <i>skin/airway-sensitizing substance</i> with “Sah”. Moreover, in this group are listed substances taken into account for skin sensitization as a toxicity endpoint by industry and other non-governmental organizations such as the Ecological and Toxicological Association of Dyes and Organic Pigments Manufacturers (ETAD), the Human and Environmental Risk Assessment (HERA). Finally, all the substances regarded as “potentially sensitizing dyes” by the Commission of the European Community for the award of the Community eco-label to textile products.
Substance for which it is not possible to exclude a sensitizing potential	Substances not classified in Annex I to Directive 67/548/EEC for which, even in the absence of any categorization by EU, ACGIH or DFG, it is not possible to exclude a sensitizing potential on the basis of reliable documents such as those published by Scientific Committee on Cosmetic Products and Non-food products (SCCNFP), the International Programme on Chemical Safety (IPCS) and the British Industrial Biological Research Association (BIBRA).
Substance for which inadequate documents are available, but it is classified by ETAD both as respiratory sensitizer and as skin sensitizer with the combined risk phrase R42/43	This group is used for substances for which papers available in the open literature and published reports give inadequate information as regards as the selected criterions, but ETAD indicates to classify them as respiratory/skin sensitizers.
Substance for which inadequate documents are available, but it is classified by ETAD as skin sensitizer (risk phrase R42)	

### Carcinogenesis evaluations

This section contains:

- a) the evaluation of the International Agency for Research on Cancer which includes the degree of evidence of carcinogenicity in humans; the degree of evidence of carcinogenicity in laboratory animals; the carcinogenesis category; the bibliographic reference of the most recent IARC monograph in which the substance was taken into consideration and which refers to the carcinogenesis category [26]; data obtained through the official website of the IARC (<http://www.iarc.fr>);
- b) the evaluation of carcinogenicity of the US Environmental Protection Agency which includes the carcinogenesis category adopted by the USEPA in accordance with the Guidelines for Carcinogen Risk Assessment published in 1986 [27], 1996 [28], 1999 [29], 2005 [30]. Data are obtained via the USEPA website ([www.epa.gov/iris/subst/](http://www.epa.gov/iris/subst/)).

### Occupational Exposure Limits

This section contains, if available, Occupational Exposure Limit values (OELs) such as:

Threshold Limit Values (TLV) set by American Conference of Industrial Hygienists (ACGIH). Three types of TLVs are defined, although not for every substance: the most common is the Time-Weighted Average (TLV-TWA). The TWA concentration is referred to a conventional 8-hours workday and a 40-hours workweek, for which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect.

For some airborne contaminants, an *excursion value* is set called *short-term exposure limit* (TLV-STEL): it is referred to a 15-minutes TWA exposure that should not be exceeded at any time during a workday, even if the 8-hours TWA is within the TLV-TWA. The TLV-STEL is the concentration for which it is believed that workers can be exposed continuously for a short period of time without suffering from 1) irritation, 2) chronic or irreversible tissue damage, 3) dose-rate-dependent toxic effects, or 4) narcosis of sufficient degree to increase the likelihood of accidental injury, impaired self-rescue, or materially reduced work efficiency.

In certain cases a *ceiling value* is designated called Ceiling (TLV-C) as the concentration that should not be exceeded during any part of the working exposure.

The designation *sensitization* when available is given referring to the potential for an agent to produce sensitization, as confirmed by human or animal data.

The *sensitizing designation* set by The Senate Commission of the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) in the workplace air when available is included in the BDS. Three types of sensitizing substances are indicated:

- skin sensitizing substances (Sh);
- respiratory organ sensitizing substances (Sa);
- sensitizing both respiratory system and skin (Sah).

This designation refers only to the organ or organ system in which the allergic reaction is manifested. The pathological mechanism producing the symptoms is not taken into account.

### UPDATING THE DATABASE

The BDS is in continuous evolution and it is regularly updated taking into account both Community Legislation (new updating of Annex I) and new scientific acquisitions. The database can be revised in the occurrence of:

- publication of an adaptation to technical progress of Directive 67/548/CEE, leading to an updating of the Annex I of the Directive 67/548/CEE. The reference is always represented by the Community Directive and not by the implementation at national level. At present the 29<sup>th</sup> ATP, published on June 16<sup>th</sup> 2004, implemented at national level on February 25<sup>th</sup> 2006, is in force [11];
- identification of new substances which can display potential sensitizing properties on the basis of the updated list of threshold limit values annually revised and published by the American Conference of Governmental Industrial Hygienists (ACGIH) and by the List of MAK and BAT values of Deutsche Forschungsgemeinschaft (DFG);
- identification of potentially sensitizing substances by the Ecological and Toxicological Association of Dyes and Organic Pigments Manufacturers (ETAD).

### FUTURE PERSPECTIVES

The BDS is a "relational" database, allowing future updating after an experimental phase, for example the search procedure can be improved also taking into account the possible comments and suggestions by the end users. For substances which have been officially classified by the EU not recently (*e.g.*, before '90) with an *endpoint* different from "sensitization", the procedure to collect scientific information, already adopted for all the substances, will be put in place. This approach will allow to detect any possible emerging sensitizing power for any substance already classified but not for sensitizing effects. The collection of sensitisation relevant information will continue. At the moment the BDS is available in Italian only, early it will be available also in English.

Finally on 27<sup>th</sup> of June 2007, the European Commission has adopted the "Proposal for a Regulation of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures, and amending Directive 67/548/EEC and Regulation EC number 1907/2006" (COM 2007 355 final). The proposed act aims at aligning the EU system of classification, labelling and packaging of substances and mixtures to the United Nations Globally Harmonised System (GHS). This is expected to facilitate global trade and harmonised communication of hazard information of chemicals

**Table 5** | *Respiratory and skin sensitisation [8, 31]*

Respiratory sensitisation		Basis for classification
<b>EU criteria</b>	<b>Xn R42</b>	Human evidence that the substance/preparation can induce specific respiratory hypersensitivity - normally seen as asthma, rhinitis and alveolitis or where there are positive results from appropriate animal tests, or in case the substance is an isocyanate, unless there is evidence that the specific isocyanate does not cause respiratory hypersensitivity
<b>GHS criteria</b>	<b>Category 1</b>	If there is evidence in humans that the substance can induce specific respiratory hypersensitivity and/or if there are positive results from an appropriate animal test
Skin sensitisation		Basis for classification
<b>EU criteria</b>	<b>Xi R43</b>	If practical experience shows that the substance/preparation may be capable of inducing sensitisation by skin contact in a <i>substantial number</i> of persons, or where there are positive results from an appropriate animal test
<b>GHS criteria</b>	<b>Category 1</b>	If there is evidence in humans that the substance can induce sensitisation by skin contact in a substantial number of persons or if there are positive results from an appropriate animal test

and to promote regulatory efficiency. Once the GHS Regulation repeals Council Directive 67/548/EEC in 2015 after a transitional period, the GHS hazard classes and categories will replace the existing classification scheme. While the EU and GHS criteria match completely for some hazard classifications, differing criteria may apply to others.

For the purpose of the present article, it should be noted that according to the GHS classification criteria [31], described in *Table 5*, substances shall be classified as:

- *respiratory sensitizers* (category 1) if there is evidence in humans that the substance can induce specific respiratory hypersensitivity, or if positive results are obtained from appropriate animal tests; or/and
- *contact sensitizers* (category 1) if there is evidence that the substance can induce sensitization by skin contact in a substantial number of humans, or positive results are obtained from appropriate animal tests.

For the respiratory or skin sensitization the GHS classification criteria are identical to those applied by directive 67/648/EEC so that the number of classified substances will not change under GHS.

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Most health hazards are covered in both classification systems and the current EU system and the GHS and are conceptually similar and deal with the same structural elements. Nevertheless, due to some differences at various levels, only for a few hazard classes an agreement between the two systems can be noted.

This is the case of respiratory or skin sensitization, if immunological contact urticaria is considered separately. For substances which cause immunological contact urticaria, the GHS recommends the classification as contact sensitizers, irrespective of their properties as respiratory sensitizers. In contrast, in the EU system this is to be considered only for substances that are not classified as respiratory sensitizers.

Therefore, in the period of transition between the present procedures and the GHS system, the information made available in these fields will be included in the BDS database in order to ensure a complete updating.

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