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Information gathering for CLP classification

Ida Marcello[a], Felice Giordano[b] and Francesca Marina Costamagna[a]
[a] *Centro Nazionale Sostanze Chimiche, Istituto Superiore di Sanità, Rome, Italy*
[b] *Dipartimento di Sanità Pubblica e Malattie Infettive, Sapienza Università di Roma, Rome, Italy*

Summary. Regulation 1272/2008 includes provisions for two types of classification: harmonised classification and self-classification. The harmonised classification of substances is decided at Community level and a list of harmonised classifications is included in the Annex VI of the classification, labelling and packaging Regulation (CLP). If a chemical substance is not included in the harmonised classification list it must be self-classified, based on available information, according to the requirements of Annex I of the CLP Regulation. CLP appoints that the harmonised classification will be performed for carcinogenic, mutagenic or toxic to reproduction substances (CMR substances) and for respiratory sensitisers category 1 and for other hazard classes on a case-by-case basis. The first step of classification is the gathering of available and relevant information. This paper presents the procedure for gathering information and to obtain data. The data quality is also discussed.

Key words: hazardous substances, European Union, information systems, classification, globally harmonized system.

Riassunto *(Raccolta di informazioni per la classificazione in accordo con il Regolamento CLP)*. Il Regolamento sulla classificazione, etichettatura e imballaggio di sostanze e miscele (CLP) considera due tipi di classificazione: la classificazione armonizzata e l'autoclassificazione. La classificazione armonizzata è decisa a livello comunitario e l'Allegato VI del Regolamento CLP contiene un elenco di classificazioni armonizzate. Le sostanze per cui non è disponibile una classificazione armonizzata devono essere autoclassificate dal responsabile della loro immissione sul mercato, sulla base delle informazioni disponibili e secondo i criteri contenuti nell'Allegato I del CLP. Il CLP stabilisce che la classificazione armonizzata verrà effettuata per cancerogeni, mutageni, tossici per la riproduzione (sostanze CMR) e sensibilizzanti respiratori di categoria 1 e per altre classi di pericolo individuate caso per caso. La raccolta di dati pertinenti disponibili rappresenta la prima fase del processo di classificazione. Questo articolo illustra la procedura per la raccolta di dati e come recuperare informazioni. Vengono inoltre esaminati aspetti relativi alla qualità dei dati.

Parole chiave: sostanze pericolose, Unione Europea, sistemi informativi, classificazione, sistema armonizzato globale.

INTRODUCTION

In the framework of Regulation (EC) no. 1272/2008 [1] (named CLP Regulation - classification, labelling and packaging), the information gathering on chemicals is mainly required by the self-classification principle. This principle, defined as *Obligation to carry out investigations*, was originally in the Article 6 of Directive 67/548/EEC [2]. The CLP Regulation reaffirmed the self-classification principle in Article 55, comma 4, as *Obligation to carry out investigation (Table 1)*.

HARMONISED AND SELF- CLASSIFICATIONS UNDER DIRECTIVE 67/548/EEC

Two different types of classification were foreseen for substances before the CLP Regulation:

- the *harmonised classification*, intended to address all the physicochemical, toxicological and ecotoxicological properties of substances and preparations which may constitute a risk during normal handling or use. It was determined at Comunitary level and was the outcome of an in-depth evaluation made by an EU Working Group of Experts (European Commission Working Group on the Classification and Labelling of Dangerous Substances), taking account of all the information available on the intrinsic properties of a substance (physicochemical, toxicological and ecotoxicological);
- the *self-classification* (or *provisional classification*), produced by the responsible for marketing those substances not included in the list of harmonised classifications but presenting anyway dangerous properties.

However, in some cases the harmonised classification was *partial* as it was addressed only to a selected hazard class; a specific *note H* was applied to these cases. The note H indicates that the classification given was only related to the dangerous property(ies) indicated by the risk phrase(s) in combination with the category(ies) of danger shown in the classification itself, and thus other hazards not included in the harmonised classification need to be addressed by the supplier of the chemical [3]. Until 2008 the partial harmonised classification regarded only specific sub-

Address for correspondence: Ida Marcello, Centro Nazionale Sostanze Chimiche, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: ida.marcello@iss.it.

Table 1 | *Self-classification principle [1, 2]*

Previous legislation Directive 67/548/EEC – Article 6	New legislation Regulation 1272/2008 – Article 55(4)
Obligation to carry out investigations Manufacturers, distributors and importers of dangerous substances which appear in the EINECS but which have not yet been introduced into Annex I shall be 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 rules laid down in Articles 22 to 25 and the criteria in Annex VI.	**Obligation to carry out investigations** […] for manufacturers, distributors and importers of substances which appear in the EINECS but for which no entry has been included in Part 3 of Annex VI to Regulation (EC) No 1272/2008 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 dangerous substances according to the rules and the classification criteria.

stances or group of substances such as certain complex coal and oil derivatives, and certain entries for groups of substances in Annex I to Directive 67/548/EEC (*e.g.* o-anisidine azodyes and o-tolidine dyes). For example in the case of petroleum derivatives the harmonised classification only addresses the carcinogenic and, in some cases, the aspiration hazards. For these petroleum substances the responsible for placing on the market have to carry out the self-classification for all other hazards, not included in their respective Annex I entries, based on the available data (*i.e.* flammability, health systemic effects and environmental hazards).

The self-classification was always required for preparations.

PARTIAL HARMONISED CLASSIFICATION UNDER CLP REGULATION

The Regulation 1272/2008, like the previous system, maintains the two different approaches to the classifications: *harmonised classification* laid down at Community level according to the classification criteria set out in Part 2-5 of Annex I to CLP and *self-classification* to be produced by the supplier through the application of the same above mentioned criteria and on the basis of available data.

The innovative principle set out by the CLP Regulation is that in the future the harmonised classification will predominantly focus on:

- substances of high concern such as carcinogens, germ cell mutagens, substances toxic for reproduction (CMRs) and respiratory sensitisers (Article 36.1 of the CLP Regulation). This limitation is due to the fact that Authorities' resources should be focused on the most and relevant hazardous properties for which expert judgment is required and for which classification gives rise to important risk management measures [4];
- moreover, harmonised classification will normally cover all hazardous properties for active substances in biocidal products (regulated under Directive 98/8/EC) and plant protection products (under Regulation 1107/2009/EC) (Article 36.2 of the CLP Regulation);
- other hazard classes or differentiations, with regard to health and the environment, could also be addressed on a case-by-case basis (*e.g.* in case of contradictory data for particular properties which need an *expert judgment*), if a justification can be provided demonstrating the need for such action at Community level (Article 36.3 of the CLP Regulation). This means that all the other hazards will be self-classified.

It follows that harmonised classification will increasingly be partial and CLP Regulation will be primarily a self-classification system for enterprises. The *Guidance on the application of the CLP criteria* places emphasis on self-classification of the substances or mixtures by manufacturers, importers or dowmstream users defining it a *core principle* [5].

This means that even for substances included in Table 3.1 and Table 3.2 of Annex VI to CLP, these harmonised classifications indicate the *minimum mandatory classification*; all the other endpoints not covered by such classification have to be investigated, searching available information and, in case of relevant data, the self-classification for these endpoints will be performed (as stated by Article 4.3 of the CLP Regulation). For example, a substance may have an harmonised classification for acute oral toxicity, but not for acute dermal toxicity. This means that a supplier would have to explore, using the information available, whether the classification criteria for acute dermal toxicity are fulfilled, and to classify accordingly [6].

The EU Commission Regulation 286/2011, consistently with the new principle regarding the partial harmonised classification introduced by the CLP Regulation, deletes note H from Annex VI [7].

Under CLP Regulation, as in the old legislation, mixtures must always be self-classified.

THE BASIC STEPS OF CLASSIFICATION

The self-classification made by the responsible for the placing on the market should follow the same criteria used by RAC (Risk Assessment Committee) of ECHA (European Chemicals Agency) for harmonised classification, set out in the Annex I to the CLP Regulation and explained in detail in the section 12 of the *Introductory guidance on the CLP Regulation* [8].

The classification process involves the following basic steps:

- gathering of all relevant available data regarding the potential hazards of the substance (or mixture) of interest;

- systematic examination and evaluation of adequacy and reliability of the gathered information to ascertain the hazard associated with the substance (or mixture);
- comparison of the information with the criteria for classification for each hazard class or differentiation within the hazard class (distinction depending on the route of exposure or the nature of the effects) checking if gathered information reveals an hazardous property and if this property is directly comparable to the respective hazard criteria in order to decide if the substance will be classified as hazardous.

It follows from the foregoing that the information gathering represents the first step of the self-classification process.

DATA FOR CLASSIFICATION AND THEIR ORIGIN

The intrinsic properties of chemicals are the information to be searched for every toxicological or ecotoxicological endpoint. Data related to physical properties, if not available in the literature, must be generated by means of experimental assays unless adequate and reliable information are already available (Article 8.2 of

Table 2 | *CLP guidance documents*

Guidance on the preparation of dossiers for harmonised classification and labeling [12]
http://guidance.echa.europa.eu/docs/guidance_document/clh_en.pdf

Language: available only in English

Updating: May 2010

Recipients: for Industry Use (manufacturers, importers and downstream users) and for Authorities Use (Member State Competent Authorities - MSCAs)

The document provides technical guidance for preparing a CLH (harmonised classification and labelling) dossier under the CLP Regulation. It gives an overview of the general process for the preparation of a CLH dossier providing detailed information on the different steps in order to prepare a CLH dossier (including the phase of information gathering) and information about the processing of the dossier once it has been submitted to the Agency.

Regarding information gathering the document focuses on additional sources such as:
- *Registration dossiers*: information can be generated as a result of dossier or substance evaluation under the REACH Regulation
- *Other available information*: information required for other regulatory purposes (*e.g.* data submitted under the Plant Protection Products and Biocidal Products Directives); information generated under internationally recognized chemical programmes for example reviews performed under the preceding EU legislation (*e.g.* Regulation (EEC) no. 793/93) by OECD, WHO, IARC, ECETOC, or by Member States
- *Information on related substances and from (Q)SARs:* information on structural analogues
- *Data on substances undergoing new testing*: for example as a consequence of a testing proposal included in the registration dossier
- *Other supporting information*

Introductory Guidance on the CLP Regulation [8]
http://guidance.echa.europa.eu/docs/guidance_document/clp_introductory_en.pdf

Language: available in all EU languages

Updating: August 2009; a new edition will be released in 2011

Recipients: mainly addressed to suppliers (*i.e.* manufacturers of substances, importers of substances and mixtures, downstream users, distributors of substances and mixtures and producers and importers of certain specific articles).

The document provides guidance on the basic features and procedures of the CLP Regulation. It describes how to carry out the self-classification. Of particular concern for information gathering, as it is focused on where find information in order to classify and label substances and mixtures, are:

Section 10. *Sources of information* and

Annex 3 - *Additional sources* such as:

in-house search

information produced for compliance with REACH

transport directives (substances)

other information sources including:
- EU information and data sources (*e.g.* ESIS- European Chemical Substances Information System and EFSA- European Food Safety Authority, for active substances of plant protection products)
- International non-EU sources: EChem Portal (from OECD), NICNAS (National Industrial Chemicals Notification and Assessment Scheme, Australia), IPCS (International Programme on Chemical Safety on INCHEM website)
- United States sources: Registry of Toxic Effects of Chemical Substances (RTECS) available from the NIOSH-National Institute of Occupational Safety and Health; US Environmental Protection Agency (EPA); IRIS (Integrated Risk Information System) available from the US EPA website; TOXNET (includes databases such as Toxline and HSDB); PubMed portal from the US National Library of Medicine.

Guidance on the Application of Regulation (EC) No 1272/2008 [5]
http://guidance.echa.europa.eu/docs/guidance_document/clp_en.pdf

Language: available only in English

Updating: August 2009; a new edition expected at the end of 2011

Recipients: for Industry Use (manufacturers or importers) and for Authorities Use (Member State Competent Authorities - MSCAs)

The document provides detailed guidance on how to carry out the self-classification: general principles of classification and labelling under the CLP Regulation as well as on the criteria for the classification and labelling of substances and mixtures and how to use relevant available information for classification purposes.

CLP Regulation) whereas it should be noted that the obligation to perform any test with respect to toxicological and ecotoxicological properties is not imposed (Article 8.1 of the CLP Regulation) and classification needs only to be made on the basis of available data.

Relevant data for the purpose of classification of a substance can be gathered by many sources according to a procedure formerly used in the 67/548/EEC Directive, reaffirmed by CLP (Article 5 of the CLP Regulation) and referred substantially to:

- technical and scientific literatures for physical properties;
- human data retrieved from a number of sources including analytical epidemiological studies, clinical studies, well documented case reports and observations; human experience such as occupational data and data from poison information units and accident databases are also taken into account;
- experimental data assays including all *in vitro* and *in vivo* testing data, obtained through standard internationally recognized methods;
- non-testing data (*e.g.* data obtained with (Q)SAR models, grouping of substances, read across, weight of evidence).

The procedure of gathering information needs to be as wide as possible and could include sources of different types such as:

- *open literature information* (primary papers, reviews, books, monographs, and reports of proceedings, meetings and conferences);
- *electronic sources* include factual data banks (containing pre-selected factual information) and bibliographic databases (providing direct access to the literature without any pre-selection and used for exhaustive searches when factual databases contain insufficient data);
- *portals* (allowing simultaneous search of multiple databases);
- *the internet* (search engines allow identification of electronic versions of a wide range of data sources);
- *websites* of various expert organizations and regulatory bodies contain useful information;
- *grey literature*, intending materials that cannot be found easily through conventional channels such as publishers. This unconventional literature includes technical reports from governmental agencies or scientific research groups, working papers from research groups or committees;
- *in house company and trade associations files*, intending unpublished information from companies, may include studies generated in-house, commissioned studies carried out by contract houses, information on type and experience in use, reports from downstream companies and customers, purchased reports from other companies, collections of published papers and reviews of published data, and safety data sheets. This kind of information may be regarded as confidential and require expertise to interpret it;
- any other data that may assist in identifying the presence or absence of hazardous properties of the substance.

Within the human data, the possibly available information on human experience, when adequate, reliable and representative, generally deserves primary attention with respect to animal experiments and testing data. It should be noted that in accordance with the Community institutions' practice, established in Annex VI to Directive 67/548/EEC and reaffirmed in CLP Regulation, information derived from extensive and consistent *practical human experience* may be considered to be sufficiently robust, by an expert judgment, in order to classify (*e.g.* for substances presenting an aspiration hazard in humans or which cause significant/severe inflammation of the skin on immediate, prolonged or repeated contact or which cause significant ocular lesions or capable of inducing a sensitisation by skin contact in a substantial number of persons). A typical example may be methanol, which has an oral LD50 in rat ≥ 5000 mg/kg while from human experience data this substance is known to cause lethal intoxications in humans (mostly via ingestion) in relatively low doses ("…minimal lethal dose in the absence of medical treatment is between 300 and 1000 mg/kg") [5].

Finally, also all previously harmonised classifications under Directive 67/548/EEC, that have been converted into CLP harmonised classification, are sources to be considered. The data source for this harmonised classifications is represented by Table 3.1 (it lists about 8000 substances officially classified by EU according to Directive 67/548/ EEC) and Table 3.2 (it lists the same substances according to CLP classification) of Annex VI to CLP Regulation amended by Regulation 790/2009 and Regulation 286/2011 [7, 9].

In case of substances subjected to registration, for which a dossier is available, the same sources have to be intended as additional sources useful in order to complete the available database.

HOW TO OBTAIN THE INFORMATION

A single exhaustive source of information does not exist because of the extremely numerous and multidisciplinary hazards to be considered for the classification (physical-chemical, health and environmental). CLP Regulation clearly affirms that for purpose of self-classification all *relevant* and *accessible* existing information should be taken into consideration. Data must be *adequate* and *accessible*. The term adequate is used to cover the reliability of the available data and their relevance for human and environmental hazard classification. *Accessible* means that, except for physical hazards for which generally substances and mixtures testing is required, data are not experimentally produced but may be obtained by a relevant scientific searching of all data which are known or which "should reasonably be expected to be known" to whom who have to carry out the self-classification. This definition presently acquires particular importance because of the remarkably high amount of

Table 3 | *REACH guidance documents relevant to CLP*

Guidance on information requirements and chemical safety assessment [13]
http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm#r20

Language: the pathfinder is available in all EU languages while some parts are available only in english

Updating: May 2008; a new edition will be released in 2011

Recipients: for Industry Use (manufacturers, importers, downstream users) and for Authorities Use (Member State Competent Authorities - MSCAs); addressed to trained persons.

Structure: consists in a package of 28 single documents including a *pathfinder* to the different elements of the guidance and two major parts:
- *Concise guidance*: focus processes and dialogues, made up of seven parts (Part A to G);
- *Reference guidance*: supporting documents containing technical and scientific details of hazard and exposure assessment (Chapters R.2 to R.20).

The guidance document gives advice on how to carry out certain steps which are common to hazard assessment under REACH and classification, where to find available information, how to assess collected data or how to use non-testing information. Expert knowledge may be required to understand and use this advice.
The parts of this Guidance, relevant for information gathering, with purpose of classification are the following:

Concise guidance - Part B: Hazard assessment [14]
http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_part_b_en.pdf?vers=20_10_08

Language: available in all EU languages

Updating: May 2008

Contains concise guidance on hazard assessment including information requirements on intrinsic properties of a substance to be registered under REACH, including information gathering, non-testing approaches and the so-called "integrated testing strategies" in order to generate relevant information for each hazard. Each of the sections in Part B corresponds to the more in-depth guidance contained in Chapters R.2 to R.10. Particularly relevant for information gathering are:

Reference guidance - Chapter R.3: Information gathering [15]
http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r3_en.pdf?vers=20_08_08

Language: available only in English

Updating: May 2008

This Guidance describes in depth collection of available information; it considers all types and sources of information that could be included in any search strategy (in house Company and trade association files; databanks and databases of compiled data; published literature; internet search engines and relevant websites; (Q)SAR models). Moreover an indicative list of major available databases and databanks is given (in Sections R.3.1 to R.3.4 distinguishing "no fee sources" and "fee based sources". The adequacy and suitability of such data through specific Integrated Testing Strategies (ITS) for each endpoint is given.

Reference guidance - Chapter R.4: Evaluation of available information [16]
http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r4_en.pdf?vers=20_08_08

Language: available only in English

Updating: May 2008

Provides guidance on how to evaluate all available information gathered; covers concepts of completeness (does the available information meet the information required for classification?) and quality (relevance, reliability and adequacy) of information.

Reference guidance - Chapter R.6: Guidance on QSARs and grouping of chemicals [17]
http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r6_en.pdf?vers=20_08_08

Language: available only in English

Updating: May 2008

Detailed guidance on non-testing approaches such as QSAR and grouping which facilitate the evaluation of the intrinsic properties of chemicals. Moreover, it provides sources in terms of software programs developed for the calculation of molecular descriptors and pertinent computational tools/databases that are either publicly or commercially available.

Reference guidance - Chapter R.7: Endpoint specific guidance This chapter contains detailed specific guidance on gathering, evaluation and, where necessary, generation of information on the physicochemical properties and the different human health and environmental endpoints which can contribute to derive appropriate information for classification and labelling of a substance. The document is divided in main sections on each endpoint which is described and for which the process of gathering and evaluation of all available data is provided. Each endpoint is described and its importance is explained in the context of human health or environmental fate. Guidance is given on how to evaluate the information that could be available for a given substance; this advice focuses to provide the criteria in order to aid the judgement and ranking of the available data for their adequacy and completeness. Practical tables give references to information sources (hard and electronic databases) for which features and limitations are discussed.

Chapter R.7a - Endpoint specific guidance for physico-chemical properties and the different human health [18]
http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r7a_en.pdf?vers=02_02_10

Language: available only in English

Updating: May 2008

In this chapter, specific guidance on meeting the information requirements on physicochemical properties and the different human health and the environmental endpoints is presented. The guidance for each specified endpoint has been developed as a stand-alone report addressing the aspects of gathering, evaluation and generation of information. Over 20 intrinsic physicochemical properties (such as melting/freezing point; boiling point; relative density; vapour pressure; surface tension; water solubility; partition coefficient in-octanol/water; flash-point; flammability; explosive properties; self-ignition temperature; oxidising properties; granulometry; stability in organic solvents and identity of relevant degradation products; dissociation constant; viscosity) and individual human health endpoints (such as skin- and eye irritation/corrosion and respiratory irritation; skin and respiratory sensitization; acute toxicity; repeated dose toxicity; reproductive and developmental toxicity; mutagenicity and carcinogenicity) are examined.

Continued

Table 3 | *Continued*

Chapter R.7b - Endpoint specific guidance for environment [19]
(http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r7b_en.pdf?vers=20_08_08).

Language: available only in English

Updating: May 2008

Are examined environmental endpoints with reference to aquatic toxicity; long-term toxicity to sediment organisms; degradation and biodegradation. Reference to pertinent databases and documents are provided.

Chapter R.7c - Endpoint specific guidance for environment and toxicokinetics [20]
http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r7c_en.pdf?vers=20_08_08

Language: available only in English

Updating: May 2008

Environmental endpoints with reference to bioconcentration and bioaccumulation; long-term toxicity to birds; effects on terrestrial organisms are examined; an Appendix describes databases on aquatic bioaccumulation. Extensive guidance on toxicokinetic data are moreover given.

scientific information available through the internet. "Reasonably be expected to be known" may includes *e.g.* classifications/evaluations of carcinogenic agents performed by institution such as IARC (International Agency for Research on Cancer) and US EPA (United States Environmental Protection Agency). These classifications, carried out in accordance with clearly specified criteria and procedures, have been always used in accordance with an institution's prior practice for substances not formally classified in Europe under Directive 67/548/EEC [10] (*e.g.* dichlorvos non classified for carcinogenicity under Directive 67/548/EEC but classified by IARC as "probable human carcinogen" group 2B which corresponds to a category 2 carcinogen under CLP Regulation).

Under CLP it is not required to perform animal testing only for the purpose of health and environmental classifications. It is however important to know where to retrieve information relevant for each classification endpoint in order to develop an appropriate searching strategy. The European Chemicals Agency (ECHA) made available a set of tools in order to facilitate the CLP Regulation application; between these a range of guidance documents providing an overall guidance for the classification have been published, freely available to access and download from ECHA's webpage (http://www.echa.europa.eu) and very useful in the phase of information gathering. These guidance documents help the data searchers to understand the range of potential sources of information and their content, structure, design and format. *Table 2* shows some of these relevant documents.

Moreover physical, health and environmental hazard assessments are an important part of the REACH registration process. For this it should be noted that some guidance documents on REACH, produced by ECHA, which describe good practices, processes and methods in order to fulfill obligations compelled by Regulation 1907/2006, are also relevant for CLP Regulation as they contain indication on how to derive adequate information on hazard assessment of substances and mixture. *Table 3* shows some of these REACH guidance documents. These guidance documents generally include methodological sections (instructions useful to set search strategies and evaluate relevancy, reliability and adequacy of the information gathered) and tables which contain a wide selection of free- or against payment information sources and describe characteristics and limits of each source giving direct links.

Following the same principles of REACH Regulation the relevant information used to produce the classification (and the labelling) of substances or mixtures must be assembled and kept available for a period of at least 10 years by the supplier after the last supply of the substance or the mixture together with any other information that suppliers are obliged to hold as specified in Article 49.1 of the CLP Regulation [1]. National Competent Authorities or the Agency (ECHA) may require the supplier to submit this information unless it is already available as part of a registration (under REACH) or a notification (under CLP). This obligation to store data applies not only to data showing that the substance is hazardous, but also to data showing that the substance is not hazardous and therefore *not classified* because it does not meet the classification criteria or is *unclassifiable* due to inconclusive data or lack of data. The principle is that the classification criteria apply to all hazardous and all not hazardous substances and mixtures as reliable data in order to decide on their hazard are needed and either a classification decision or a reason for not classifying must be recorded for each classification endpoint.

SOME CONCLUSIVE OBSERVATIONS

It is not possible to use only one source of information for classification purposes. All the data sources contained in the guidance documents in *Table 2* and *Table 3* represent a good starting point in the step of gathering information, but an integration between the different sources is needed in order to obtain adequate overall data. In particular, account should be taken of their possible limits as, of course, quality and comprehensiveness of these sources are widely different: for example some classification endpoints need high specialization (*e.g.* some data base particularly focused in

aquatic toxicity or in environmental fate). On the other hand the problem regards not only the quality but also the quantity of data contained in the information sources. Some information sources contain a relatively restricted number of chemicals but high quality data in contrast to other sources including a large number of chemicals but low quality data. For example in the case of acute health hazard classification the Registry of toxic effects of chemical substances (RTECS) compiled by NIOSH (National Institute of Occupational Safety and Health) represents the world's most extensive collection of numerical toxicological data as contains more than 160 000 chemicals while Hazardous substance data bank (HSDB) contains over 5000 chemicals. In this case it is important to know that information in HSDB is referenced and peer reviewed by the Scientific Review Panel (SRP), a Committee of experts in the major subject areas within the data bank's scope while for RTECS the editor declares unequivocally that the data are taken from primary source without any evaluation in terms of correctness, validity and quality of the studies. Nevertheless in some cases RTECS is the only available source of data.

Other limits that can be presented by the different sources are due to:

- *type of information used*. For example while using a transport classification for a substance not included in Annex VI to CLP, one should be aware that the transport classification does not include all of the GHS categories for physical, health and environmental hazards, so the absence of a transport classification does not mean that the substance should not be classified under CLP [8];
- *multiple data from different information sources*. In this case data obtained according to validated test methods (specified in Annexes V and VIII of Directive 67/548/EEC, or REACH Annex X methods; or OECD) and/or in compliance with the principles of GLP (good laboratory practice) (or equivalent) standard take precedence. However a certain flexibility in their evaluation is needed: the optimum indeed would be the availability of updated and GLP complying data, but if a study is not conducted in accordance with GLP it does not necessary mean the study is not suitable. An expert judgment could be necessary in these cases [5];
- *conflicting data from different sources, e.g.* from reviews (often acute toxicity data). In this case it is essential to retrieve the original source. It is also necessary in this case to choose reliable data (in accordance with guidelines, and/or GLP and scientifically relevant);
- generally, primary emphasis shall be placed upon *existing human experience* and data, followed by animal experience and testing data, followed by other sources of information. However evaluation of available gathered information must be performed on a case-by-case basis and with *expert judgement*;
- *conflict between humans and animals findings* shall be solved evaluating the quality and reliability of the evidence from both sources;
- moreover attention should also be paid to *information contained in the internet as it can be highly volatile.* According to the Article 49 of the CLP Regulation the gathered information must be adequately kept possibly with the search strategy.

Finally the problem of lack of data remains the key problem (*e.g.* specific aquatic toxicity data are lacking for many substances; chronic toxicity data are lacking for some substances in the NLM online databases; for several substances, essentially not relevant information are located in available open sources).

Data gap on available information on the chemical hazards has been well document in the last decades. Several studies performed by European Commission and US EPA equally have demonstrated that basic chemical data, even for high priority volume chemicals (HPVC) is only minimally available, stimulating different initiatives and policies [11]. When data are lacking CLP classifications can be developed by read-across and weight of evidence strategies but a prominent contribution is expected under REACH regulation as additional information on (hazardous) properties of existing substances will come directly from data contained in registrations, from which a progressive relevant improvement could be obtained in available information.

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Conflict of interest statement

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