RESPONSABILIDAD® INTEGRAL COLOMBIA

Globally Harmonized System of Classification and Labeling of Chemicals - GHS:

Data collection guidance on the classification of hazards

Ambiente

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ICCA International Council of Chemical Associations

Globally Harmonized System of Classification and Labeling of Chemicals - GHS: Data collection guidance on the classification of hazards

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Data collection guidance on the classification of hazards
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The final version will be ready in September 2023;
nevertheless, the contents of the guidance will be the same".**

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Fabian Benzo Moreira, International GHS Expert Consultant, is the technical lead and author of this guidance document. Furthermore, it has been reviewed and drafted by Ana María Ocampo Gómez, Expert Doctor in Chemical Risk Management and Manager of Responsabilidad Integral Colombia; with the support of the Group of Chemical Substances, Respel and UTO of the Minambiente and the COP Project Team.

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PROLOGUE

The use of chemical substances in Colombia has been increasing in manufacturing processes, extractive activities and services, of which the main source is imports and, to a lesser extent, national production. For this reason, the country has been working on the search for an integrated management of chemical substances in their life cycle focused on the prevention, reduction, management and control of risks and disasters associated with the use of these substances.

This path has been accompanied by compliance with the commitments of international conventions that have been ratified in Colombia, such as those of Basel, Rotterdam, Stockholm, Minamata and SAICM. SAICM is a multilateral global initiative, in which the governments of different countries participate, as well as supranational organizations; it is led by the United Nations Environment Program (UNEP) and the World Health Organization (WHO). In Colombia, the Ministry of Environment and Sustainable Development and the Ministry of Health and Social Protection have worked together to implement national strategies to adopt SAICM goals and advance in their fulfillment.

Within the scope of SAICM implementation, the project "*Strengthening national governance for SAICM implementation in Colombia*" *was developed,* with its main outcomes being the update (second edition) of the National Profile of Chemical Substances, the first edition of which had been developed in 1998, and the National Action Plan for the Management of Chemical Substances in *Colombia (2013-2020)*. Subsequently, the project "*Support for the application of SAICM and the Globally Harmonized System for Classification and Labeling of Chemical (GHS) in Colombia*" was executed between the years 2013 to 2017. UNITAR was in charge of its implementation and the Ministry of Environment and Sustainable Development was in charge of its execution.

The second edition of the National Profile of Chemical Substances in Colombia, published in 2013[1] and its update published in 2017[2], present the general situation in relation to the different stages of the management of chemical substances in Colombia. It raises the need to formulate new regulatory and public policy frameworks in the country to

1 López Arias, A., Suárez Medina, O. J., & Hoyos, M. C. (2012). *Perfil Nacional de Sustancias Químicas en Colombia* (2a edición). Ministry of Environment and Sustainable Development, United Nations Industrial Development Organization - UNIDO.

2 Perfil nacional de sustancias químicas en Colombia. Vol. II: Actualización de los capítulos 2 y 3, con énfasis en sustancias de uso industrial [electronic resource] /Suárez Medina, Oscar Javier. Narváez Rincón, Paulo Cesar. Bogotá. D.C.; Colombia. Ministry of the Environment and Sustainable Development, 2017.

strengthen the comprehensive management of the risk associated with the use of such substances, through the collection and dissemination of information; identificationand classification of hazards; risk assessment and management; and inspection, surveillance and control activities in the stages of importation, production, transportation, storage, use, marketing or distribution and disposal of chemical substances, with the purpose of achieving prevention, reduction or control of risk situations and their materialization in accidents that have impacts on health and the environment.

Another advance the country has made in the management of chemical substances, was the 2016 CONPES 3868 document, which represents the national policy for the management of risk associated with the use of chemical substances. The purpose of this policy is to "*integrate, in a coherent manner, the risk management processes and the stages of the life cycle of chemical substances to cover the broad spectrum of problems associated with their use, seen from the perspective of two objects of interest: (i) chemical substances and (ii) the facilities in which they are used.*"

This policy presents the guidelines for the development of the Program for the Management of Industrial Chemical Substances and the Program for the Prevention of Major Accidents in *Colombia*. The CONPES 3868 document establishes the development of cross-cutting instruments for the strengthening of institutional, financial and legal capacity for risk management associated with the use of industrial chemicals and the prevention of major accidents. As part of these cross-cutting instruments, the implementation in Colombia of the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) is proposed.

The GHS is adopted in Colombia with the issuance of Decree N$_{o}$ 1496 of 2018 by the Ministry of Labor, the Ministry of Health and Social Protection, the Ministry of Commerce, Industry and Tourism, and the Ministry of Agriculture and Rural Development. From 2019 to 2022, resolutions and guidelines have been issued by the competent authorities on the subject, for the implementation of the GHS in the labor, agriculture and transportation sectors.

The first step for the implementation of the GHS is the classification of hazards. The classification of chemical hazards according to the GHS is not a simple process and presents a number of difficulties. A preliminary study conducted in the United States showed that one-third of the one hundred Safety Data Sheets - SDS analyzed for ten high-production volume chemicals showed classification errors.

Furthermore, the official GHS classifications available for the same substance commonly do not match.[3]

According to the GHS, the first step in classification is to collect relevant, reliable and suitable data. This step is critical to achieving the safe use of chemicals, since it has an effect on the information to be communicated to workers, users and consumers, through labels and SDS.

In Colombia and other Latin American countries, considerable efforts have been made to develop capacities for the adoption and implementation of GHS, but there is still a considerable way to go. Existing capacities to carry out hazard classification of chemicals are still limited.

The purpose of these guidelines is to provide information, references and guidance for the collection of reliable data for the classification of chemical hazards according to the GHS. The guidelines and tools provided in this document reflect a way of solving data collection (not the only one), the best known from practice and the one that is considered to be the best adapted to the current reality of Colombia in this matter.

3 BlueGreen Alliance and Clearya True Health Hazard Project; United States of America (2022).

ABBREVIATIONS

ACS: American Chemical Society.

GLP: OECD Principles of Good Laboratory Practice.

C: Dose/Concentration which produces a significant, non-lethal acute toxic effect.

CAS: Chemical Abstract Service.

EC_{50}: Effective concentration fifty.

ECr_{50}: Effective concentration fifty in terms of the reduction of the growth rate.

EC_x: Concentration which causes x% of the response.

LC_{50}: Lethal Concentration fifty.

CWOE: Concentration Without Observed Effects.

BOD_5: Biological Oxygen Demand over a 5-day period.

LD_{50}: Lethal Dose fifty.

COD: Chemical Oxygen demand.

ECHA: European Chemicals Agency.

BCF: Bioconcentration Factor.

SDS: Safety Data Sheet.

FP: Flash Point.

HSNO CCID: Hazardous Substances and New Organisms Chemical Classification and Information Database (New Zealand).

IARC: International Agency for Research on Cancer.

ICCA: International Council of Chemical Associations.

LOAEL: Low Observed Adverse Effect Level.

log Kow: Octanol/water partition coefficient

NITE-J: National Institute of Technology and Evaluation (Japan).

NITE-J CHRIP: NITE Chemical Risk Information Platform.

NOAEL: No Observed Adverse Effect Level.

OECD: Organization for Economic Co-operation and Development.

ILO: International Labor Organization (United Nations).

ONAC: Organismo Nacional de Acreditación de Colombia [National Accreditation Organization of Colombia].

UNIDO: United Nations Industrial Development Organization.

BP: Boiling Point.

UNDP: United Nations Development Program.

UNEP: United Nations Environment Program.

QSAR: Quantitative Structure-Activity Relationship.

REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals.

RTMP: Recomendaciones relativas al Transporte de Mercancías Peligrosas [Recommendations regarding the Transport of Hazardous Goods].

GHS: Globally Harmonized System of Classification and Labeling of Chemicals.

SAICM: Strategic Approach to International Chemicals Management.

EU: European Union.

UNECE: United Nations Economic Commission for Europe.

UNITAR: United Nations Institute for Training and Research.

1. INTRODUCTION

1.1 Objective and scope

The purpose of these guidelines is to provide knowledge and tools for obtaining quality data, which supports the classification of hazards according to the Globally Harmonized System for Classification and Labeling of Chemicals - GHS. They are based on the 6th revised edition (2015) of the United Nations' "purple book",[4] which was adopted in Colombia through Decree 1496 of 2018.

These guidelines seek to complement ***step 1 of obtaining data***, a necessary condition for the classification of hazards of substances and mixtures, when this process is based both on data on the mixture itself or on the components. Within its scope, the *steps 2 (data analysis)* and *3* (decision on classification) of the classification process[5] are not considered.

Notwithstanding the above, these guidelines are very useful for the interpretation of data when obtained from a source that includes data analysis.

1.2 Target audience

These guidelines are targeted at those in charge of the hazard classification of chemicals, with training and experience in occupational safety and health, the environment, knowledge of the GHS ("purple book") and knowledge of the United Nations Model Regulations for the Transport of Dangerous Goods ("UN Orange Book") [6].

Having met the above requirements, the extent to which these guidelines can be used may vary for each individual, depending on the following points:

- Knowledge and handling of databases of information on chemicals.

4 Available at: https://unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev06/Spanish/ST-SG-AC10-30-Rev6sp.pdf.

5 The description of the three steps mentioned is presented in paragraph1.4 of these guidelines.

6 Available in: (Vol. 1) https://unece.org/sites/default/files/2022-01/ST-SG-AC10-1r22s_Vol1_WEB.pdf
(Vol. 2) https://unece.org/sites/default/files/2022-01/ST-SG-AC10-1r22s_Vol2_WEB.pdf

- Knowledge and experience of physical, toxicological, ecotoxicological and environmental testing methods for chemicals.
- Prior experience of the classification of chemicals, regardless of the system used.

1.3 GHS

The GHS is an internationally agreed system for standardizing the classification and communication of chemical hazards.

The GHS includes the following elements:

- Criteria for the classification of substances and mixtures according to their physical hazards, health hazards and environmental hazards.
- Requirements for the communication of chemical hazards, through labels and SDS.

While the GHS is primarily intended for use by governments as the basis for regulations on chemical in different countries, it also contains sufficient information and guidance for those who are in charge of the classification, labeling and production of SDS of chemicals.

The GHS is described in a document known as the United Nations "purple book", with the first edition being published in 2003, and updates of the same produced every two years. All the editions of the GHS can be found on the UNECE website.[7]

The (2021) review document 9 (2021) of the "purple book" consists of four parts and ten annexes. The four parts are:

- Part 1. Introduction (5 chapters).
- Part 2. Physical hazards (17 chapters, one for each class of physical hazard).
- Part 3. Health hazards (10 chapters, one for each class of health hazard).
- Part 4. Environmental hazards (2 chapters, one for each class of environmental hazard).

For a better use of these guidelines, and considering their scope, the most relevant parts of the "purple book: to be considered are the following:

7 Available at: https://unece.org/about-ghs.

- Part 1, chapter 1.3 (classification of hazardous substances and mixtures).
- Part 2, all chapters:
  - » Section: definitions.
  - » Section: classification criteria.
  - » Section: decision-making process and complementary indications.
- Parts 3 and 4, all chapters:
  - » Section: definitions.
  - » Section: classification criteria for substances.
  - » Section: decision-making process and complementary indications.
- Annex 9 (Guidance on hazards to the aquatic environment).
- Annex 10 (Guidance on transformation/dissolution of metals and metal compounds in aqueous media).

1.4 Regulatory background of the GHS in Colombia

In 2011, the Ministry of Environment and Sustainable Development - MinAmbiente, held the national workshop in Bogotá on the theme "*Basic elements and experiences in the implementation of the Globally Harmonized System on classification and labeling of chemicals*", carried out within the scope of the project "Strengthening Governance for the implementation of SAICM in Colombia", signed between the Ministry of Environment and Sustainable Development and UNIDO, which was an initial approach to the GHS issue in Colombia, from the Government.

The workshop, targeted mainly at personnel from public entities, industry and academia, provided an overview of the GHS, identified some of the main advantages and limitations of adopting this system in the sectors of

interest to Colombia, and gave an idea of how it could be implemented, based on the experiences of other countries in the region on the subject.

On the other hand, the national government, in its National Development Plan for 2014-2018, expressed its intention to join the Organization for Economic Cooperation and Development (OECD), therefore it had to start strengthening the instruments and mechanisms for environmental management and particularly chemicals management, in light of the guidelines (Decisions and Recommendations) emanating from the Chemicals Committee of that organization.

As part of the OECD membership process, in May 2013, the national government conducted an Environmental Performance Review (EPR) with OECD experts on biodiversity, waste and chemicals, among others. As a result of this evaluation, the OECD issued a series of recommendations to be adopted by the national government, including the need for the country to implement as a priority a strategy for the application of the Globally Harmonized System for the Classification and Labeling of Chemicals (GHS).

In December 2013, the project "*Support for the implementation of the GHS and SAICM in Colombia*" was signed, under an agreement between the United Nations Institute for Training and Research - UNITAR, the Ministry of Environment and Sustainable Development, and the Presidential Agency for International Cooperation in Colombia - APC. Its most relevant activities included the structuring of a National Strategy for the implementation of the GHS; the preparation of a situation and gaps analysis in the GHS; the development of information guidelines for the industry on classification and on communication of the hazards covered by the GHS; and GHS training workshops targeted at different stakeholders.

Subsequently, in 2014 and 2015, Minambiente worked inter-institutionally on the consultations of the National Strategy document and in the formulation of an intersectoral plan for the implementation of the GHS at the national level.

In 2018, and as previously mentioned, Decree 1496 was issued, adopting the GHS in Colombia. This decree establishes that the GHS will be implemented for chemicals used in workplaces, chemical pesticides for agricultural use, chemicals in the transport stage, and chemicals targeted at consumer use.

In Colombia, the sector related to chemical pesticides for agricultural use is regulated by Decision 804 of 2015 of the General Secretariat of the

Andean Community of Nations[8], which entered into force on May 1 of that year, and which amended Decision 436 of 1998. In 2019, the amendment of the Andean Technical Manual for the registration and control of chemical pesticides for agricultural use was approved, with Resolution 2075 of 2019, which establishes the provisions for the gradual implementation of the GHS in the labeling of such pesticides. Subsequently, in 2020, Resolution 75487 of the Instituto Colombiano Agropecuario [Colombian Agriculture and Fishing Institute] - ICA was issued, which establishes the provisions for the gradual implementation in the labeling of chemical pesticides for agricultural use.

Subsequently, the Ministries of Labor and Health and Social Protection issued Resolution 0773 of 2021 to comply with the implementation of the GHS for chemicals used in the workplace. This resolution defined the actions to be carried out by employers for the implementation of the GHS in workplaces and issued other provisions on chemical safety.

In 2022, External Circular 20221010000177 of the Ministry of Transportation was issued, which presents the guidelines for the implementation of the GHS in chemical and hazardous goods transportation operations.

Finally, in order to promote compliance with the regulations associated with the GHS in some sectors, MinaAmbiente, with the support of UNDP, has worked on identifying technical assistance needs for its implementation with organizations in the sectors where processes of substitution of substances classified as persistent organic pollutants (POPs) for alternative substances will be carried out.

1.5 Classification of hazards according to the GHS

The classification of a chemical involves comparing quality data about product characteristics with GHS criteria.

The classification of hazards is a process which consists of 3 stages:

1. Data collection.
2. Data analysis.
3. Decision on classification.

Each of these three steps will be described below.

8 Andean Community of Nations. Ruling 804 of 2015. Modification of the Decision 436 (Andean Regulation for the Registration and Control of Chemical Pesticides for Agricultural Use). [Online] Available at: http://www.comunidadandina.org/Normativa.aspx?GruDoc=07

1.5.1 Data collection

The first step in hazard classification is to obtain data that is, in the first instance, comparable to the GHS classification criteria.

Examples:

Class of hazard	GHS Criteria
Flammable liquids	FP, BP
Acute toxicity	LD_{50}, LC_{50}
Acute hazards to the aquatic environment.	LC_{50}, EC_{50}, ECr_{50}

Data is originated using different methods and can be obtained from a variety of sources, as presented in Chapter 2 of these guidelines.

1.5.2 Data analysis

Data analysis consists of determining the quality of these. This process is integrated in 3 steps:

1. Step 1: Evaluation of the relevance of the data.
2. Step 2: Evaluation of the reliability of the data.
3. Step 3: Evaluation of the suitability of the data.

In some cases, data analysis is simple, but in others, it is not, and an expert judgment is required. One of these cases is where there is more than one piece of data and this leads to a different classification.

For example, two values of LD_{50} for the same chemical product using the same route, but in different species:

- LD_{50} (oral, rats) = 100 mg/kg, justifies classification in category 3 of acute toxicity.
- LD_{50} (oral, mice) = 5 mg/kg, justifies classification in category 1 of acute toxicity.

In the last data, the test species (mice) is not the one considered by the GHS criteria (rats), and it is known that mice are a more sensitive species than rats in acute oral toxicity tests.

However, if this data is considered reliable, it should not be discarded a priori and should be subject to further analysis, which could justify classification in category 1, category 2 or confirm the data in rats.
According to the GHS, only good-quality data can be used for classification, i.e. relevant, reliable and suitable data.

1.5.3 Decision on classification

The decision on classification involves comparing the quality data, resulting from the above steps, with the GHS classification criteria.

The classification criteria are included in the chapter for each of the hazard classes in the "purple book".

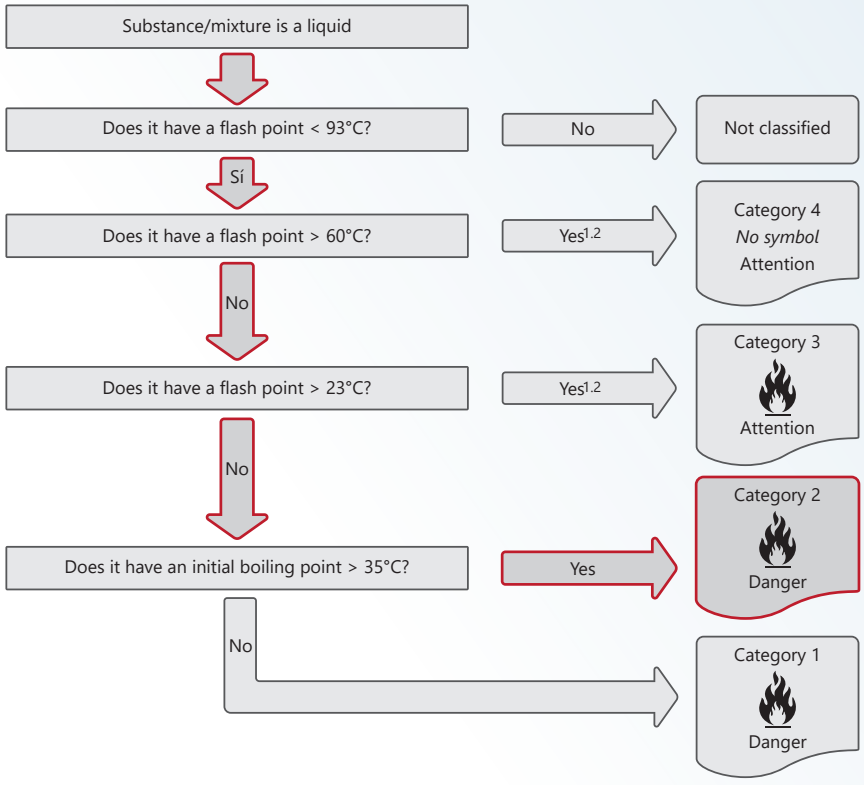
For example, the classification criteria for flammable solids (chapter 2.7 of the "purple book"), both substances and mixtures, are included in paragraph 2.7.2. On the other hand, the classification criteria for carcinogenicity (chapter 3.6 of the "purple book") are included in paragraph 3.6.2 for substances and paragraph 3.6.3 for mixtures.

Also, at the end of each chapter, decision-making procedures are included, consisting of flow charts that facilitate "auto-classification", once the necessary data is available.

For example:

Data	**State:**	→	Liquid chemical product
	Flash point:	→	20ºC.
	Boiling point:	→	80ºC.

Decision-making procedure 2.6 for flammable liquids



Classification result: flammable liquids, category 2.

There are two possible outcomes that can arise from comparing the quality data to the GHS criteria (two possible classifications):

- Not hazardous, when the data does not comply with the criteria.
- Hazardous, when at least one piece of data complies with the criteria.

It is important to note that in the latter case, the classification must include both the hazard class(es) (nature of the hazard) and the corresponding hazard category (degree of hazard).

Examples:

Incorrect classification	Correct classification
Flammable liquids	Flammable liquids, category 2.
Acute toxicity	Acute toxicity (cutaneous route), category 3.
Hazards to the aquatic environment	Short-term hazards (acute) to the aquatic environment, category 1.

1.6 Classification of substances and mixtures

The GHS makes a clear distinction between the classification of substances and that of mixtures.

The classification of substances, for all hazard classes, is based exclusively on data on the substance itself or on data on substances with similar chemical structures.

In the case of mixtures, the classification depends on the hazard class and there are different strategies for this process. These strategies are presented below, in order of preference.

a. Data on the mixture itself (applicable to all types of hazards).
b. Principles of extrapolation (applicable to health and environmental hazard classes only).
c. Data on the components of the mixture (applicable only to health and environmental hazard classes).

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2. DATA

2.1 Introduction

As mentioned in the previous chapter, the classification is based on the comparison of data on the chemical and the GHS criteria.

While GHS does not require testing, the quantity and quality of the data are critical aspects that will directly affect the outcome of the classification, either by omitting, underestimating or overestimating hazards).

At this point, it is important to realize that incorrect classification can lead to accidents, exposure and contamination, with serious consequences, and to reflect on the main motivation for implementing the GHS:

- Solely to comply with applicable legal requirements.
- To provide the highest quantity and quality of information to the users and consumers of the chemical product.

The amount of data available will largely depend on the main motivation for implementing the GHS and on the aspects cited below:

- **The chemical product:**

  There are chemical products for which a lot of information is available (chemical products that have been in use for a long time or that are subject to some form of registration), while for others, there is little or even no information (e.g. new and/or not so commercially relevant chemical products). In general there is far more data for substances than for mixtures.

- **The type of data:**

  Some data is easy or relatively easy to obtain, as is the case for certain physicochemical properties (e.g. pH) and some animal tests (e.g. skin irritation test in rabbits). However, other data is obtained through long and/or costly tests (e.g., carcinogenicity tests in animals, determination of BCF), which often do not justify or limit their performance.

- **Availability of own data:**

  Companies with their own capacity to conduct certain tests or that have the ability to afford tests performed by third parties will have a greater amount of data available, compared to smaller companies or companies with limited resources for these types of activities.

- **The accessibility to third-party data or data generated by third parties:**

  The accessibility of third-party data or data generated by third parties depends on the information of the persons in charge of the classification on possible data sources and, in some cases, on the economic possibility of the company to access certain databases that they have to pay for.

In relation to data quality, this depends mainly on three aspects:

1. **Relevance of the data.**
2. **Reliability of the data.**
3. **Suitability of the data.**

The three aspects mentioned above are presented in more detail in paragraph 2.4. of these guidelines.

The data can be classified into different forms. For the purposes of these guidelines, the data is classified taking into account the following aspects, which are explained in detail in paragraphs 2.2 to 2.5:

- *Classes of data.*
- *Methods used to obtain data.*
- *Quality of the data.*
- *Data sources.*

2.2 Data classes

There are four categories of data classes, according to the properties or parameters to which they relate. These categories are:

- Physicochemical.
- Toxicological.
- Ecotoxicological.
- Ecological (viability and environmental destination).

Listed below are the data that fall into each category and, highlighted in blue, those that are directly related to the GHS criteria.

2.2.1 Physicochemical data

- Appearance/Physical state/ Color
- Smell
- Melting point/ Freezing point
- Boiling point
- Density
- Distribution of particle size (granulometry)
- Vapor pressure
- Log K_{ow}
- Water solubility
- Solubility in organic and fatty solvents
- Superficial tension
- Flash point
- Spontaneous ignition point
- Decomposition temperature
- Auto-accelerated decomposition temperature
- Lower and upper flammability limits
- Explosivity
- Oxidizing properties
- pH
- Kinematic viscosity

2.2.2 Toxicological data

1. Toxicokinetics, metabolism and distribution
2. Acute toxicity (LD_{50}, LC_{50}, C)
3. Skin corrosion/irritation
4. Eye irritation
5. Respiratory sensitivity
6. Skin sensitivity
7. Toxicity of repeated doses (LOAEL, NOAEL)
8. Genotoxicity
9. Carcinogenicity
10. Toxicity for reproduction (LOAEL, NOAEL)

2.2.3 Ecotoxicological data

1. Short-term aquatic toxicity (CL_{50}, CE_{50}, CEr_{50})
2. Long-term aquatic toxicity (CSEO, CE_x)
3. Toxicity for microorganisms
4. Endocrine disruptors in aquatic vertebrates
5. Toxicity to other aquatic organisms
6. Toxicity of sediments
7. Terrestrial toxicity

2.2.4 Ecological data

- Stability (phototransformation in air, hydrolysis)
- Biodegradation in water (BOD_5, COD)
- Biodegradation in sediments
- Biodegradation in soil
- Bioaccumulation (BCF)
- Transport and distribution (adsorption/desorption, Henry's Law Constant)

2.3 Data collection methods

Data on chemicals can be obtained using different methods, such as human observations, tests, extrapolation from analogous chemicals and mathematical models.

Accordingly, data is classified into five categories (listed in order of relevance or preference) as described below:

- Observations in humans.
- *In vivo tests*.
- *In vitro/ex vivo* tests.
- Physicochemical tests.
- *In silico* tests.
- Extrapolation of analog chemicals.

That is, at equal or comparable data quality, data from observations in humans is the most relevant and will take precedence over any other data.

2.3.1 Observations in humans

This data is used exclusively for health hazards.

Examples:

- Clinical trials (e.g. skin sensitization test).
- Epidemiological studies (e.g. carcinogenicity).
- Accidents in the workplace (for example, skin corrosion/irritation).

2.3.2 In vivo tests

These are tests performed on living organisms (animals, plants). The name *in vivo* refers to the fact that the test is performed inside the organism itself. They are used for health and environmental hazards.

In the case of animal testing, the GHS emphasizes animal welfare, not only to alleviate the stress and suffering to which animals are subjected, but also to reduce the use of animals in testing.

For this reason, animal testing should be avoided whenever possible and, in this case, tests that require smaller numbers of animals or cause them less suffering should be preferred.

Examples:

- Acute toxicity testing in rats (acute toxicity).
- Irritation tests in rabbits (skin corrosion/irritation, severe eye damage/eye irritation).
- Algae growth inhibition tests (acute aquatic toxicity).
- Daphnia reproduction tests (chronic aquatic toxicity).

2.3.3 In vitro/ex vivo tests

These are tests that are performed outside a living organism, on tissue, organ or cell samples. They are used for health hazards.

In vitro studies consist of the analysis of samples in isolation and incubated in solution, creating the conditions for the processes of interest to occur, and even changing these conditions to achieve different responses. The name *in vitro* responds to the fact that this type of assay is normally performed in Petri dishes or test tubes.

In *ex vivo* studies, the test conditions are similar to those of a biopsy, with minimal alteration of natural conditions and do not necessarily require incubation.

One difference between *ex vivo* and *in vitro* assays is that the former have a maximum duration of 24 hours. If the tests/assay lasts longer than 24 hours, it is an *in vitro* assay.

Ex vivo *tests or assays* are less developed than *in vitro* assays, are more expensive, but provide results that are more similar to *in vivo* results.
In vitro/ex vivo *data* can be used to replace or supplement data with *in vivo* assays, such as, for example, in a weight of evidence approach, as will be discussed below.

Examples:
- Skin corrosion testing on rat skin discs (skin corrosion/irritation).
- Reconstructed human epidermis test (skin corrosion/irritation).
- Mammalian chromosomal aberration test (germ cell mutagenicity).
- Gene mutation test in mammalian cells (germ cell mutagenicity).
- Ames bacterial reverse mutation test (germ cell mutagenicity).

2.3.4 Physicochemical tests

As the name implies, they consist of laboratory analyses to determine the physical and chemical properties and characteristics of the product. They are mainly used for physical hazards, but also for some health and environmental hazards.

Examples:
- Determination of the flash point (flammable liquids).
- Dynamic viscosity (aspiration hazard).
- pH measurement and examination of acid/alkaline reserve (corrosion/skin irritation).
- Determination of log K_{ow} (bioaccumulation potential).

2.3.5 In silico tests

The *in silico* tests, known as QSAR (Quantitative Structure-Activity Relationship), are predictions made from mathematical models that relate one or more quantitative parameters obtained from a chemical structure to a quantitative measurement of a property or activity.

These tests are carried out using computers and can be used to predict physicochemical, biological and environmental properties of compounds from knowledge of their chemical structure.

Unlike *in vitro/ex vivo* tests, QSARs are generally not recommended to replace *in vivo* or physicochemical tests. Instead, QSAR predictions can be used as supporting information, e.g., to support assay results that have not been performed according to the OECD GLP or according to accepted guidelines, provided that these predictions match experimental results.

Specific reference to the scope of QSARs is made in the GHS in the 6th edition, paragraph 4.1.2.13 and Annex A9.6, on hazards to the aquatic environment and in the 9th edition, paragraph 3.2.2.6, on the corrosion/skin irritation hazard class.

Several QSAR models are available for different properties, some open access and some restricted access.

It is recommended to run all available QSAR models for a given property, particularly when the models use different algorithms. Consistency between predictions obtained from scientifically validated and independent QSAR models increases confidence in the predictions.

In addition to QSAR models, the OECD and ECHA have developed a free tool called the QSAR Toolbox.[9] In any case, whether they are QSAR models or tools, certain knowledge and experience is required for their proper use and correct interpretation of the results.

Examples:

- Prediction of the flash point: T.E.S.T. (USA EPA) (flammable liquids).[10]
- Prediction of corrosive and irritating effects on the skin: ToxTree (JRC) (skin corrosion/irritation).[11]
- Prediction of LC50 (fish, 96h): DTU (Denmark) (short-term hazards to the aquatic environment).[12]
- Prediction of the log K_{ow}: EPI Suite – KOWWIN (USA EPA) (long-term hazards to the aquatic environment).[13]

9 Available at: https://qsartoolbox.org/.

10 Available at: https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test

11 Available at: http://toxtree.sourceforge.net/

12 Available at: https://qsarmodels.food.dtu.dk/

13 Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

2.3.6 Extrapolation of analog chemicals

This procedure is based on the grouping into categories of chemicals with similar physicochemical, toxicological, ecotoxicological and/or ecological properties or that follow a common pattern as a result of structural similarity.

When a chemical can be assigned to a certain category because of some similarity with the members of that category, it is possible to predict its properties from the common properties of that category.

Data obtained by extrapolation from analog chemicals can be used to replace *in vivo* or physicochemical assays.

Examples:

- Fatty acids: the longer the chain length, the higher the log K_{ow} (long-term hazards to the aquatic environment).
- Compounds containing Cr^{6+}-: allergens (respiratory or skin sensitization).
- Hg-containing compounds: toxic to the environment (acute hazards to the aquatic environment).

2.4 Quality of the data

The quality of a piece of data is the result of a three-step evaluation process:

1. **Relevance:** first step, which is to determine the extent to which the data is relevant to the classification.
2. **Reliability:** consists of assessing and determining the reliability of each of the pieces of data in terms of the clarity and plausibility of the findings.
3. **Suitability:** the last step, which consists of assessing the weight of evidence for each piece of data and determining its usefulness for classification purposes. The most useful data is that which has been assigned the highest weight (most relevant and reliable data).

According to the GHS, only good-quality data can be used for classification, i.e. relevant, reliable and suitable data.

2.4.1 Relevance of the data

For the purpose of assessing the relevance of the available data, the following aspects should be considered, among others:

- Is **the product being tested representative of the product to be classified?** Physical states, concentrations and purities of substances and compositions of mixtures should be considered to ensure such representativeness. For example, ammonia gas is flammable, but ammonium hydroxide is not.

- **What was the procedure used to obtain the data?** The relevance of the data is subject to the order of preference established in paragraph 2.3 of these guidelines. That is, data from observations in humans are the most relevant. For example, an irritation test in rabbits (*in vivo* test) will be more relevant than an irritation result obtained by QSAR.
- **Have you studied the appropriate species in accordance with the GHS criteria?** For example, GHS criteria for acute toxicity using an oral route are based on an LD_{50} in rats. An LD_{50} in dogs can rarely be extrapolated to rats and, in this case, there will be a significant margin of error.
- **Is the route of exposure used in the test relevant?** For example, inhalation is not a likely route of exposure in non-volatile products that are only handled under normal conditions.
- **Is the mechanism of action that is evident in animals also evident in humans?** Some effects are specific to an animal species. For example, 2-butoxy ethanol produces an increased incidence of hemangiosarcomas in the liver of male mice, but the mechanism (hemolysis) is not relevant to humans.

  In order to assess the relevance to humans of data originating from animal studies, it may be important to have in the available information on the toxicokinetics of the substance, both in humans and in the animal species used.
- **Were appropriate doses/concentrations tested?** The appropriate doses/concentrations are those at which it is possible to determine unequivocally whether or not classification is warranted and, if so, to assign the hazard category. For example, for acute oral toxicity, the doses that determine the limits of each of the categories are: 5, 50, 300 and 2,000 mg/kg pc.
- **Were the critical parameters influencing the GHS criterion adequately considered?** For example, in the skin corrosion/irritation tests in rabbits, one critical parameter is the observation time (24, 48, 72 hours and 14 days). A single corrosion/irritation test on rabbits with a duration of only one hour cannot normally be used for classification purposes (unless a well-marked corrosive effect is evident).

2.4.2 Reliability of the data

Data reliability is a key aspect of the classification process and relates essentially to the way in which the study was conducted. Without knowledge of how the study was conducted, all other considerations may be irrelevant.

The reliability of the data depends on the following factors:

- **The testing method.**
- **The proven ability of the laboratory to perform the test method.**
- **The test report. A reliable report should include, at least:**
  - » The origin and characterization of the substance or mixture being tested (concentration, purity, physical characteristics).
  - » A detailed description of the test matrix (e.g., animal species, plant species, type and strains of bacteria).
  - » A detailed description of the experimental procedure, including whether deviations from the test method occurred, the causes, and the resolution of such deviations.
  - » The record of the raw (unprocessed) data.
  - » The results obtained, with the corresponding units and confidence intervals.
  - » Discussion and interpretation of the results.
  - » Conclusions.

Different approaches have been proposed to determine the reliability of data. One of the most widely used is that of Klimisch *et al* (1997), to assess the reliability of data from toxicological and ecotoxicological studies. However, this approach can also be extended to physicochemical and environmental studies.

According to this approach, data is classified into different categories, with a scoring system from 1 to 4, including the following criteria:

1.- Reliable without restrictions.

Data, mostly according to OECD GLP, obtained from:

- Testing directives (OECD, etc.)
- Methods comparable with the above.
- Methods according to national standards (EPA, ASTM, EC, DIN, etc.).

2 - Reliable with restrictions.

Data, mostly not generated under OECD GLP principles, obtained from:

- Well-documented assays that comply with scientific principles.

- Test guidelines without detailed documentation, but sufficient for evaluation.
- Test guidelines with acceptable deviations.

3 – Not reliable.

Data obtained from:

- Unvalidated methods.
- Studies with insufficient documentation for evaluation.
- Methods that do not meet important criteria of currently validated methods.
- Studies with significant methodological differences.
- Inadequate test matrix (e.g., chemical, animal species, etc.).

4 – Cannot be assigned

- Studies for which only the abstract is available.
- Data published in secondary literature (reviews, tables, books, etc.).

2.4.3 Suitability of the data

Suitability determines the usefulness of the available data for the purpose of hazard assessment, i.e., whether the available information allows for clear decision-making regarding compliance with the GHS classification criteria.

The assessment of the suitability of data is performed by applying a weight-of-evidence approach, which considers the weight of evidence obtained from at least two independent studies.

In the GHS, specific importance is attached to the weight of evidence for classification (see paragraph 1.3.2.4.9 of the "purple book"). According to this paragraph, the weight of evidence should take into account:

- All data obtained, whether the results are positive (justifying classification) or negative (not justifying classification).
- The relevance and reliability of the data.

According to the above, relative weights are assigned to each of the data. The most relevant and reliable data is assigned the highest weight.

ECHA has categorized the data into four categories, according to suitability:

- "Key": refers to data with sufficient weight to justify the classification.
- "Supporting": refers to data of lesser weight than the key data, but which is consistent with the key data and supports the classification.
- "Weight of evidence": refers to the remaining data considered in the weight-of-evidence approach, whether or not it justifies the ranking.
- "Disregarded": refers to data discarded and not considered in the weight-of-evidence approach.

Expert judgment may be needed to assess and determine the suitability of the data, particularly to determine key data.

Below are some **guidelines** for assigning data to one of the adequacy categories.

- Reliable human and animal data can be considered key, supporting, or weight-of-evidence data.
- Reliable *in vitro/ex vivo* assay data and reliable physicochemical assay data is usually considered supporting data, although in certain instances, it may be considered key data.
- Reliable QSAR data may be considered supporting or weight-of-evidence data, but never key data.
- The data obtained from extrapolation of reliable analog chemicals can be considered key data or support data.
- Data obtained by either method may be considered disregarded, particularly if it is unreliable.

Table 1 includes, as guidance, the result of a study on 349 pieces of data for 60 REACH-registered substances, which shows the relationship between the suitability and reliability of the data.[14]

Table 1.

Suitability	Reliability			
	1	2	3	4
Key	**78%**	27%	0%	0%
Support	21%	**65%**	20%	27.5%
Weight of the evidence	1%	2%	0%	2.5%
Unknown	0%	0%	14%	0%
Not specified	0%	6%	**66%**	**70%**

Examples:
Determination of the suitability

1. Acute toxicity via oral route.
   Data 1: observation in humans, reliability 3 (does not justify the classification).
   Data 2: testing on animals, reliability 1 (justifies classification).
   Determination of the suitability:
   Data 1 → Weight of the evidence
   Data 2 → Key

2. Bioaccumulation
   Data 1: *in vivo* BCF assay, reliability 1 (justifies classification).
   Data 2: log K_{ow} determination assay, reliability 1 (justifies classification).
   Determination of the suitability:
   Data 1 → Key
   Data 2 → Support

2.4.4 Examples

Examples of actual ethanol data used for REACH registration purposes, classified according to their class, reliability and suitability, are presented in Table 2 below (by clicking on the name of the data, you will go directly to the data report).

14 Ingre-Khans E., Ågerstrand M., Beronius A. and Rudén C. *Toxicol. Res., 2019, 8, 46.*

Table 2.

Data	Class	Method	Reliability	Suitability
Flash point	Physicochemical	Extrapolation of analog chemicals	2	Key
Carcinogenicity	Toxicological	Observations in humans	4	Support
Germ cell mutagenicity	Toxicological	*In vitro/Ex vivo*	2	Weight of the evidence
Toxicity in algae	Ecotoxicological	*In vivo*	3	Unknown
Biodegradation	Ecological	*In silico*	2	Support

2.5 Data sources

According to the source from which the data is obtained, it is possible to classify it into:

- Own data (first or second party).
- Third-party data or data generated by third parties (third party).

2.5.1 Own data

Data - owned by the organization - obtained from one of the following sources:

a. Knowledge of its products.

b. Actual experience.

c. Tests carried out within the organization itself.

d. Tests contracted to third parties

In the first three sources, the data is generated by the organization itself (first-party data). In the case of source d), the data is generated by a third party contracted by the organization (second-party data). In all cases, the data is owned by the organization.

Examples:

- Information on the purity of substances and exact composition of mixtures.
- Effects demonstrated from accidents suffered by workers (e.g. corrosive, irritant, sensitizing effects).
- Properties measured in the company's quality control laboratory (e.g. pH, density, dynamic viscosity).
- Tests contracted to external laboratories (e.g., flash point, acute oral toxicity, acute toxicity to crustaceans).

2.5.2 Third-party data or data generated by third parties

This consists of data - not owned by the organization - obtained from third parties. It may be freely accessible or restricted (access to the data requires a license or payment).

Examples:

- Databases (OECD, IARC, GESTIS, HSDB, TOXNET, etc.).
- Supplier information (SDS, individual queries).
- Competitor information (SDS, shared registration data).
- Literature, such as, for example, books, manuals, articles, etc. (Merck index, Bretherick manual, etc.).

3. TESTS/ ASSAYS

3.1 Introduction

When data is obtained from tests/assays, whether *in vivo*, *in vitro/ex vivo*or physicochemical, certain GHS requirements and some additional practical guidance related to test methods must be considered.

It is important to consider these requirements and guidance when wishing to obtain data from an in-house source or to assess third-party data.

When it is a first-party test, the organization should first assess whether it has all the resources needed to conduct the test in accordance with the applicable requirements.

When the test is a second-party test, the organization should clearly specify all the applicable requirements and guidance in the terms of the offer and contract with the testing service provider.

When the test is a third-party test, the organization should assess the test method and the degree of deviation from the test method to determine the reliability of the data (see paragraph 2.4.2).

A fundamental aspect of any test is the report, which should contain all the information necessary to properly interpret the test results for classification of the chemical according to the GHS (see paragraph 2.4.2).

The GHS requirements and testing guidance vary for physical hazards and for health and environmental hazards.

3.2 Physical hazards

For physical hazards (part 2 of the "purple book"), the GHS determines the test to be used for each hazard class. Therefore, such tests are a requirement of the GHS.

In other words, when an organization needs, or chooses, to perform a test to classify a physical hazard according to the GHS, it is not free to choose the test method. The test must be the one that is determined by the GHS.

The criteria for classifying physical hazards in accordance with the GHS are based on the classification criteria in the **RTMP** - Model Regulations ("orange book").

The Model Regulations state that testing should be performed in accordance with the Manual of Tests and Criteria. [15]

This manual is a United Nations publication, which complements both the "orange book" and the "purple book". The manual is periodically updated by the Committee of Experts on the Transport of Dangerous Goods and in the GHS.

The manual of tests and criteria is divided into five parts:

- **Part I.** Provisions relating to explosive substances and articles.
- **Part II.** Provisions relating to self-reactive substances, organic peroxides and polymerizing substances.
- **Part III.** Provisions relating to aerosols; desensitized explosives (solely in relation to transport); flammable liquids; flammable solids; pyrophoric liquids and solids; substances which, when in contact with water, release flammable gases; oxidizing liquids and solids; chemically unstable gases and gas mixtures; substances corrosive to metals; and Class 9 substances and articles of for transport (ammonium nitrate fertilizers, lithium metal and lithium ion batteries); and ammonium nitrate-based-solid fertilizers.

15 Available at: https://unece.org/fileadmin/DAM/trans/danger/publi/manual/Rev7/Manual_Rev7_S.pdf.

- **Part IV.** Test methods relating to transport equipment.
- **Part V.** Classification procedures, test methods and criteria relating to sectors other than transport.

Additionally, the manual has 11 appendices.

Each test consists of the following sections:

- Introduction.
- Apparatus and materials.
- Procedure (with relevant remarks and data to be extracted).
- Test criteria and assessment method of results.
- Examples of results.
- Figures (schematic diagram and/or photos of the apparatus, among others).

The tests for classifying most of the GHS physical hazard classes consist of tests included in the tests and criteria manual, and are referred to in each chapter of the "purple book".

The tests established by the GHS based on methods not included in the tests and criteria manual solely refer to two hazard classes (flammable gases and oxidizing gases).

Table 3 below indicates for each GHS physical hazard class the reference to the relevant part of the test manual and criteria or the test method prescribed by the GHS, as appropriate.

Table 3.

GHS Class of physical hazard	Test(s)
Explosives	Manual – Part I
Flammable gases	ISO 10156:2010 IEC 60079-20-1 ed 1.0 (2010-01) DIN 51794
Aerosols	Manual – Part III (Section 31)
Combustion gases	ISO 10156:2010
Pressure gases	Tests are not established
Flammable liquids	Manual – Part III (Section 32)
Flammable solids	Manual – Part III (Section 33.2)
Substances and mixtures which react spontaneously (self-reactive)	Manual – Part II

...continues.

GHS Class of physical hazard	Test(s)
Pyrophoric liquids	Manual – Part III (Section 33.3)
Pyrophoric solids	Manual – Part III (Section 33.3)
Substances and mixtures undergoing spontaneous heating	Manual – Part III (Section 33.3)
Substances and mixtures which, in contact with water, release flammable gases	Manual – Part III (Section 33.4)
Combustion liquids	Manual – Part III (Section 34)
Combustion solids	Manual – Part III (Section 34)
Organic peroxides	Manual – Part II
Substances and mixtures corrosive to metals	Manual – Part III (Section 37)
Desensitized explosives	Manual – Part III (Section 32, Section 33.2)

The content of active substance(s) and diluent(s) must be stated in the test report with an accuracy of at least ±2% by mass. This report must also indicate as accurately as possible the existence of factors that can significantly influence the test result, e.g. humidity.

All deviations from the prescribed test conditions must be described and recorded in the test report.

3.3 Health hazards and environmental hazards

In contrast to physical hazards, the GHS does not prescribe uniform test methods for health and environmental hazards.

In principle, an organization is free to choose the test method, as long as it is performed in accordance with internationally recognized scientific principles.

However, since the GHS criteria for health and environmental hazards are aligned with the OECD Guidelines for the Testing of Chemicals, it is appropriate to use these guidelines for testing because:

- It contributes to the reliability of the data (see paragraph 2.4.2 of these guidelines).
- It facilitates the interpretation of the results and the decision on classification.

Example:

Skin corrosion/irritation

According to Table 3.2.2 of the "purple book", one of the criteria for classification of a chemical as a skin irritant is the mean value for erythema/rash or for edema in at least two out of three animals at 24, 48 and 72 hours after patch removal.

According to this criterion, there are at least three factors to consider in the test:

- The number of animals tested (3 animals)
- The observation periods (24, 48 and 72 hours after patch removal).
- The effects to be observed and their assessment (erythema/rash and edema).

According to note b) of the same table, the endpoints are understood as described in OECD guideline 404.

Therefore, if the test is conducted according to this guideline, the results obtained are directly compared with the GHS criteria and the decision on classification is normally straightforward.

If a test is conducted according to another guideline that considers a number other than 3 animals, where observations are not recorded in one or more of the established periods (24, 48, 72 hours), one or both of the effects to be considered (erythema/rash and edema) are not observed, and the assessment of these effects is performed with criteria which are different from those described in OECD guideline 404, the interpretation of the results may be very difficult or even impossible.

The OECD Guidelines for the Testing of Chemicals are developed with the assistance of experts from regulatory agencies, academia, industry, environmental and animal welfare organizations, and are continually expanded and updated to ensure that they reflect state-of-the-art science and techniques.

The OECD Guidelines for the Testing of Chemicals[16] are divided into five sections:

- **Section 1.** Physicochemical properties.
- **Section 2.** Effects in biotic systems.
- **Section 3.** Environmental fate and behavior.
- **Section 4.** Effects on health.
- **Section 5.** Other testing directives.

16 Available at: https://www.oecd.org/env/ehs/testing/oecdguidelinesforthetestingofchemicals.htm.

The sections relevant to GHS are section 1, section 2 and section 3 (hazards to the aquatic environment) and section 4 (hazards to health).

All the OECD directives include, amongst others, the following points:

- Testing principles.
- Detailed testing process.
- Calculation and interpretation of results.
- Information which must be included in the testing report.

Tables 4 and 5 respectively present the OECD Guiding Principles for each of the health and environmental hazard classes (guidelines marked with * are cited in the "purple" book).

Table 4.

Class of health hazard	OECD Guideline	
	in vivo	*in vitro/ex vivo*
Acute toxicity Specific target organ toxicity - Single exposure	402 403 420 423 425 433	
Skin corrosion/irritation	404*	430* 431* 435* 439*
Serious eye injuries/eye irritation	405*	437* 438* 460*
Respiratory and cutaneous[(a)] sensitivity	406* 429*	
Germ cell mutagenicity	474* 475* 478* 485* 486* 489*	471* 473* 476* 483* 488* 490*
Carcinogenicity	451 453	

Class of health hazard	OECD Guideline	
	in vivo	*in vitro/ex vivo*
Toxicity for reproduction	414* 416* 421* 422* 443*	
Specific target organ toxicity - repeated exposure	407 408 410 411	
Aspiration hazard [(a)]		

(a) There are currently no recognized and validated methods available.

Table 5.

Class of hazard to the aquatic environment	OECD Guideline	
	in vivo	*in vitro/ex vivo*
Short-term (acute)	201* 202* 203* 221*	
Long-term (chronic)	201* 210* 211* 305*	107* 117* 123* 301* 306*

3.4 Carrying out tests/assays

In some cases, the performance of a test is a regulatory requirement and the organization is obliged to carry it out. This refers to the tests required for the registration of pesticides.

Where there are no regulatory requirements, the decision about whether to conduct a test should be inspired by a principle of responsibility based on:

- The ethical obligation to provide as much reliable information as possible about the hazards of the chemical being provided, in order to preserve the health of people, the environment and property.
- The right of workers and consumers to know.

When deciding to conduct a test, an organization should ask itself at least the following questions:

- How will this be done? (method)
- Who is going to do it? (laboratory)
- How much does it cost?

3.4.1 How will this be done?

The choice of the method for conducting the test should follow the provisions established in paragraphs 3.2 and 3.3. The method determines the following aspects, among others:

- Who will carry out the test?
- The duration of the test.
- The amount of product needed.
- The cost of the test.

3.4.2 Who will carry it out?

One of the biggest problems in Colombia for testing is the availability of laboratories with the capacity to perform the tests.

A laboratory can demonstrate its ability to perform a test if it has one of the following accreditations for that test:

- OECD GLP Principles.
- ISO/IEC 17025:2017 "General requirements for the competence of testing and calibration laboratories".

It is interesting to note at this point that, as an OECD member country, Colombia must adhere to the Mutual Acceptance of Data (MAD) system of this organization.

The MAD establishes that test data generated in any OECD member or full adherent country, in accordance with OECD test guidelines and OECD GLP principles, is accepted in member or full adherent countries for evaluation purposes and other uses related to the protection of human health and the environment.

Since 2015, the Organismo Nacional de Acreditación de Colombia [National Accreditation Body of Colombia] (ONAC) has been working

jointly with the Ministry of Commerce, Industry and Tourism, the Ministry of Environment and Sustainable Development, and with the support of UNIDO Safe+, in the implementation of the roadmap established for the country's adherence to the MAD and adoption of the OECD GLP. This roadmap established the necessary steps to achieve the recognition of ONAC as the Colombian National Monitoring Authority (NMA) before the OECD, through Decree 1595 of 2015. Subsequently, Resolution 2581 of 2017, a benchmark for the adoption of OECD GLP in the country, in which the voluntary nature of its application is also determined.

After its designation as NMA, the ONAC created and implemented the National Monitoring Plan with the advisory support of Safe+. There, the general framework was defined to verify compliance with OECD GLP in potential testing entities in the country and thus establish the basis for offering the OECD GLP recognition services in Colombia.

As of the date of publication of this document, the application by ONAC for OECD recognition and adherence to the MAD is still pending, which requires a prior inspection of at least two (2) testing entities. Currently, there are no testing entities recognized by the OECD GLP in Colombia.

A search engine for Colombian laboratories, managed by the National Quality Subsystem (SICAL)[17], has recently been made available. An inventory of laboratories with analytical capabilities for the classification of chemicals according to the GHS at the MERCOSUR level is also available.[18]

17 Available at: https://buscalab.sical.gov.co/unificado/.

18 Available at: http://ghs-sga.com/capacidades-analiticas-laboratorios/.

This inventory of laboratories was developed under an IDB project and includes the laboratories with the capacity to perform the tests required by the GHS for each hazard class in each MERCOSUR country (Argentina, Brazil, Chile, Paraguay and Uruguay).

The inventory also includes whether the laboratory has OECD GLP and/or ISO/IEC 17025 accreditation.

The choice of laboratory conditions, among other aspects, the time (shipment of samples), the cost of the test, which includes the price of the laboratory and the cost of freight of the sample(s) to the laboratory.

3.4.3 How much does it cost?

The costs vary depending on the laboratory location and credentials.

Ideally, more than one quotation should be requested and the cost/benefit ratio of each one should be evaluated, prioritizing confidence in the result provided.

There is no point in performing a test, no matter how inexpensive it may be, if the result provided is unreliable.

In addition, when an organization decides to contract the performance of a test, it must consider:

- Safety during transport and handling of the samples sent for testing. In this regard, there must be compliance with the applicable requirements of the RTMPs, particularly proper packaging of the samples, and the SDS(s) of the products to be tested must be supplied.
- The requirements to be included in the specifications or purchase contract for the service. This is an important aspect to ensure that the test and the deliverables comply with the expectations and for eventual future claims in the event of discrepancies or failure to comply by the laboratory providing the testing service.

Examples:

Requirements to be included in a test specification.

1. **Test:** Determination of the flash point.
   Purpose: Classification of the agreement with the GHS.
   Method: ASTM D 56-05.
   Product: Product name (SDS attached).
   Physical state: Liquid, viscosity 12 cp.
   Laboratory requirements (attach proof):
   - ISO/IEC 17025 accreditation with requested test included in the scope.
   - Experience in the testing method: 5 tests(minimum).

2. **Test:** Acute toxicity per inhalation.
   Purpose: Classification of compliance with the GHS.
   Method: OECD Guideline 433.
   Product: Product name (SDS attached).
   Physical state: Liquid
   Route of exposure: Aerosol.
   Laboratory requirements (attach proof):
   - OECD GLP and/or ISO/IEC 17025 accreditation with requested test included in the scope.
   - Experience in the testing method: 3 tests (minimum).

Upon receipt of the report, it must be carefully reviewed to verify that the test was performed as specified and that the report contains all the information necessary to perform the classification.


popup {
position: absolute;
top: 0;
left: 0;
width: 100%;
height: 100%;
z-index: 10;
popup .fancybox-slide--iframe .fancybox
max-width: 100%;
Social {
only screen and (min-width: 992px
sideBanner a {
height: 330px;
width: auto;
sideBanner a img {
height: 100%;
width: auto;

4. DATABASES

4.1 Introduction

It is usually not possible to have one's own data for all GHS hazard classes applicable to a given chemical, whether these are first- or second-party data.

In this context, third-party data becomes particularly relevant for the ensuring the most complete possible classification of a chemical. In fact, often third-party data is the only data available, and the classification of a chemical is based exclusively on this type of data.

The most widely used and reliable sources for obtaining third-party data are databases, therefore knowledge and good management of these is a critical aspect in the classification process.

A good database is one that guarantees the collection of quality data (relevant - reliable - suitable) or, at least, allows us to assess the quality of the data obtained, in accordance with the stipulations of paragraph 2.4.

It is important to keep in mind that the databases include information exclusively for chemical substances, not for mixtures (see definition of mixture in chapter 1.2 of the "purple book"). According to paragraph 1.5, the classification of a mixture from data on its components is only possible for health and environmental hazards, not for physical hazards.

Therefore, information obtained from databases may be useful for classifying the physical, health and environmental hazards of a substance and the health and environmental hazards of a mixture.

In the latter case, a set of tools established by the GHS must be used to carry out the classification of a mixture based on the data on the components of the mixture.

Such tools include the principles of extrapolation, addition formulas and summation methods.

These tools are beyond the scope of these guidelines, but are detailed in each of the chapters in parts 3 and 4 of the "purple book".
In summary, data obtained from databases can be used for classification of substances (in a straightforward manner) and for classification of health

and environmental hazards of mixtures, provided that the composition of the mixtures is known and any of the GHS tools mentioned above can be applied.

4.2 Classification of databases

There are numerous chemical databases, which can be classified according to:

- **The type of access**
  - » Free.
  - » By subscription.

An example of a subscription database is SciFinder^{n} of the Chemical Abstract Service (CAS) of the American Chemical Society (ACS).[19]

- **The type of information they provide.**
  - » GHS Classifications.
  - » Properties of chemical substances.

Only open access databases are included in these guidelines.

In paragraph 4.4, the following GHS classification databases will be presented:

- ECHA – C&L (EU).
- NITE-J (Japan).
- HSNO CCID (New Zealand).

In paragraph 4.5, the following chemical substance properties databases shall be presented:

- ECHA – REACH (EU).
- IARC (International Agency for Research on Cancer).

Paragraph 4.6 also presents the OECD eChemPortal chemicals portal, which provides access to numerous databases.

19 Available at: https://www.cas.org/solutions/cas-scifinder-discovery-platform/cas-scifinder/content?gclid=CjwKCAjwm8WZBhBUEiwA178UnD23AXjyg3KnrqLfP2VMO76w02jZzvvYoL65N6YjVTCdBeg0C_NcShoCwJcQAvD_BwE

4.3 Searching for information in the databases

There are different ways to search for information in databases:

- By the name of the substance.
- By number that identifies the substance (CAS, EC, UN, etc.).
- Via the chemical formula of the substance.

In general, the simplest and safest way to search for information in databases is by an identifying number, the most universal and widely used one being the CAS number.

In any case, once information is accessed, it should be verified that it corresponds to the desired substance, regardless of the search method,

4.4 GHS classification databases

4.4.1 ECHA – C&L (EU)

ECHA - C&L[20] is a database, within the ECHA portal, consisting of a public catalog containing information on classification and labeling of notified and registered substances marketed in the EU, including harmonized

20 Available athttps://echa.europa.eu/es/information-on-chemicals/cl-inventory-database

classifications according to Annex VI of Regulation (EC) 1272/2008 (CLP Regulation).

The registration of chemicals in the EU is governed by Regulation (EC) 1907/2006, known as REACH, which is currently based on the 7th edition of the "purple book".

According to the GHS building block approach (paragraph 1.1.3.1.5 of the purple book), REACH excludes the following categories of hazards in the GHS:

- Flammable liquids, category 4.
- Skin corrosion/irritation, category 3.
- Serious eye injuries/ ocular irritation, category 2B.
- Aspiration hazard, category 2.
- Acute hazard to the aquatic environment, categories 2 and 3.

Therefore, the fact that none of these hazards are listed in the substances found in the ECHA-C&L Inventory should not necessarily be interpreted as meaning that the substance does not present these hazards.

On the other hand, this application of the REACH building block approach may lead to differences in classification with other classifications that have not excluded any hazard categories from the GHS, as will be discussed later in this same paragraph.

The database can be accessed in two different ways:

- Directly through the link at the footer of the page.
- Through the following route (Figure 1):
  - » Main page of the ECHA: https://echa.europa.eu/es/home.
  - » "Chemical Information" tab.
  - » "CLP" → "Classification, Labeling and Packaging".

Once the database is accessed, to start the search for the desired substance, click on LC Inventory and the search menu opens (Figure 2).

The search menu allows searching by:

- Name of the substance.
- Identifier number (CAS No., CE No. which is an EU-specific numeric identifier).

Figure 1.

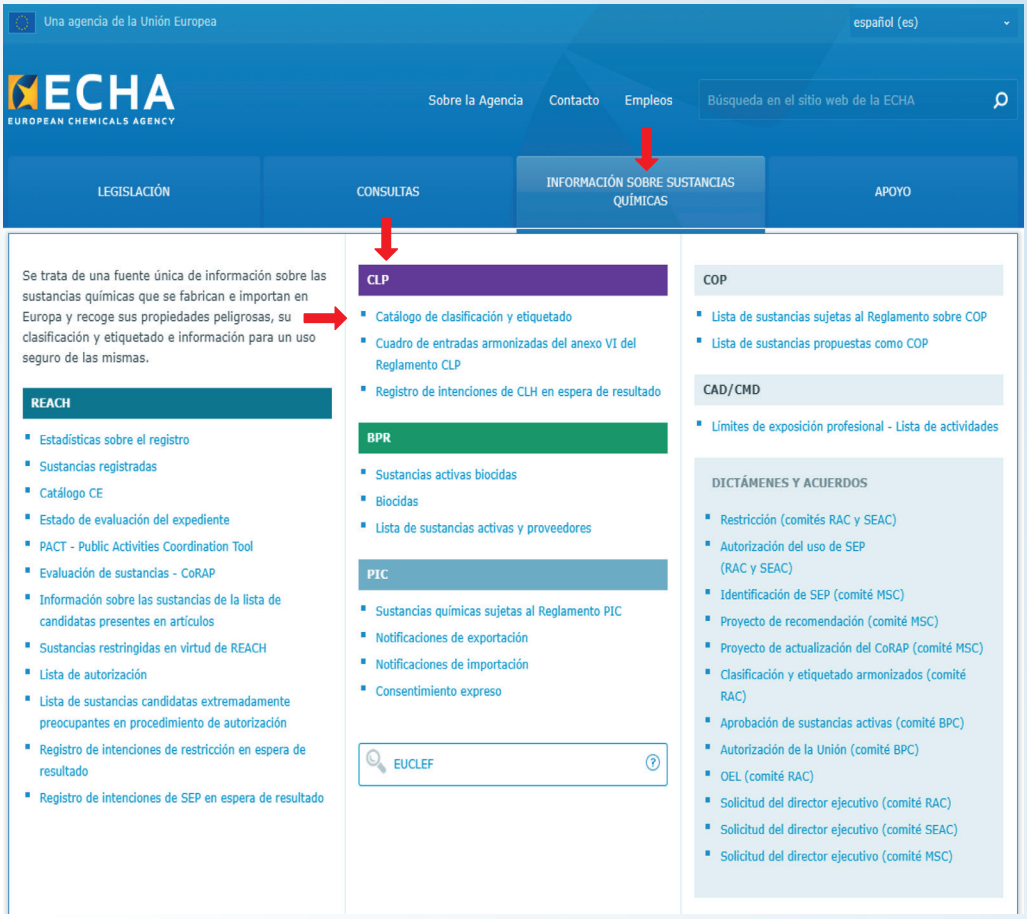
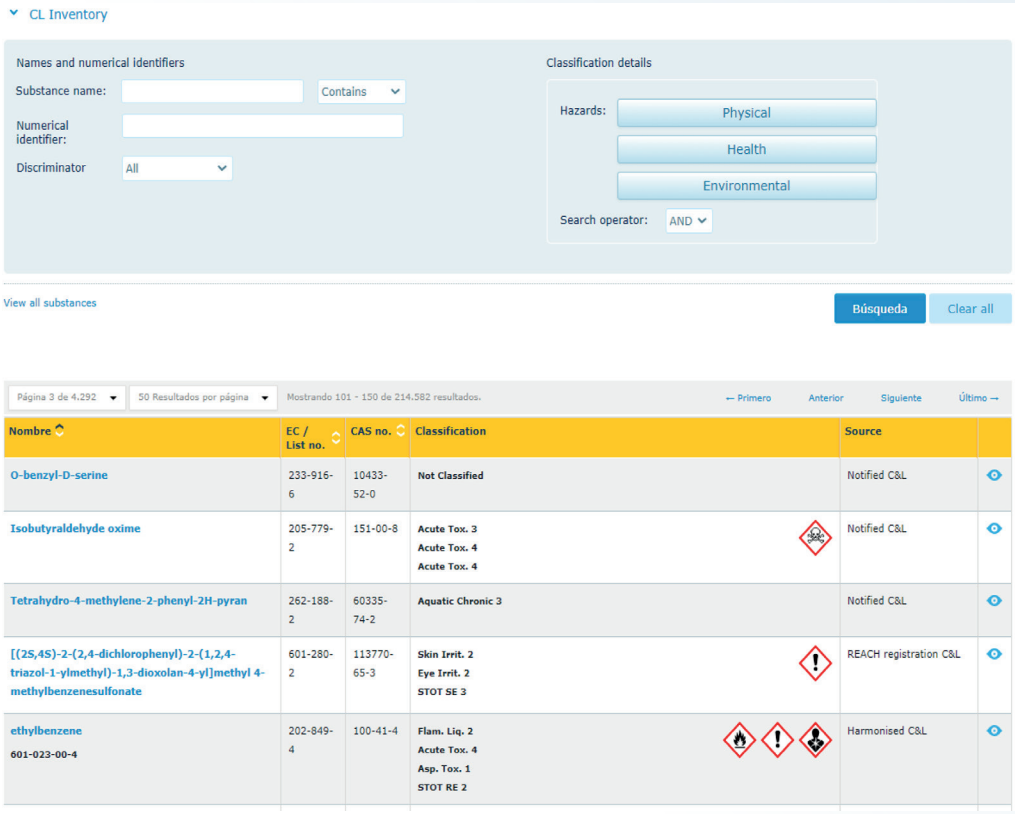


Figure 2.



As seen in Figure 2, the catalog includes six columns.

- Name of the substance.
- CE no.
- CAS no.
- Classification (according to the GHS).
- Source (source of information in accordance with its situation status in the REACH):
  - » Notified C&L.
  - » REACH registration C&L.
  - » Harmonized C&L.

The last column has no heading and always contains the following symbol . When you click on this symbol, it takes you to the summary of notifications for the substance.

The "Source" column refers to the registration status. It is important to clearly understand the difference between these types of status, as this will ensure that the information provided in this database is properly used.

"Notified C&L" Substances. These are substances notified by manufacturers, and not yet registered under REACH. The notification process requires manufacturers to propose a classification for the substance. ECHA compiles these proposals and groups them together. This information is available in the summary of notifications.

The classification listed in the inventory reflects the classification proposed in the largest number of notifications. There is no public data which supports this classification.

It is important to note that this classification does not constitute an official EU classification and is therefore not mandatory. However, the proposed set of classifications may be useful as a guideline to establish which data should be given particular attention in the substance classification process.

For example:

Substance: 1,3-dichloropropane (CAS 142-28-9)
From the ECHA-C&L catalog:

Nombre	EC / List no.	CAS no.	Classification	Source
2,2,2-trifluoroethyl trifluoroacetate	206-985-5	407-38-5	Flam. Liq. 2 Skin Corr. 1B	Notified C&L
4-nitrophenyl dihydrogen phosphate	206-353-9	330-13-2	Acute Tox. 4 Skin Irrit. 2 Eye Irrit. 2 STOT SE 3	Notified C&L
1,3-dichloropropane	205-531-3	142-28-9	Flam. Liq. 2 Aquatic Chronic 3	Notified C&L

https://echa.europa.eu/es/information-on-chemicals/cl-inventory-database/-/discli/details/1664

The link takes us to the notifications summary, which includes all the proposed classifications grouped together.

Summary of Classification and Labelling

Notified classification and labelling

General Information

EC / List no.	Name	CAS Number
205-531-3	1,3-dichloropropane	142-28-9

Notified classification and labelling according to CLP criteria

Classification		Labelling			Specific Concentration limits, M-Factors	Notes	Classification affected by Impurities / Additives	Additional Notified Information	Number of Notifiers	Joint Entries	
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code(s)	Pictograms, Signal Word Code(s)							
Flam. Liq. 2	H225	H225		GHS02 Dgr				State/Form	16		View details
Aquatic Chronic 3	H412	H412									
Flam. Liq. 2	H225	H225		GHS02 Dgr					6		View details
		H225		GHS02 Dgr					4		View details
Flam. Liq. 3	H226	H226		GHS07 GHS02 Wng				State/Form	3		View details
Acute Tox. 4	H332	H332									
Not Classified									1		
Flam. Liq. 2	H225	H225		GHS07 GHS02 Dgr				State/Form	1		View details
Skin Irrit. 2	H315	H315									
Eye Irrit. 2	H319	H319									

As you can see in the notifications summary:

- There are 10 different proposed classifications (only the first 5 are included in the figure above).
- The classification listed in the catalog is the one that received the highest number of notifications (16) and is as follows (highlighted in red in the above figure):
  - » Flammable liquids, category 2.
  - » Chronic hazard for the aquatic environment, category 3.
- The other notifications propose different classifications. For example, there is only one notification that proposes the classification of the substance as non-hazardous (marked with the arrow in the above figure).
- Considering all the proposed classifications, specific attention should be paid to obtaining data for the following hazard classes:
  - » Flammable liquids.
  - » Acute toxicity.

- » Skin corrosion/irritation.
- » Serious eye injuries/ ocular irritation.
- » Specific target organ toxicity, single exposure (respiratory irritant).
- » Chronic hazard to the aquatic environment.

"REACH registration C&L" substances. These are substances notified and registered under REACH. As for the "Notified C&L" substances, the classification in the inventory reflects the classification proposed in most notifications, but for these substances, there is public data available to support the classification (access to this data will be discussed in paragraph 4.5.1).

It is important to note that this classification does not constitute an official EU classification either and is therefore not mandatory.

For example:

Substance: cyclopentene (CAS 142-29-0)
From the ECHA-C&L catalog:

Nombre	EC / List no.	CAS no.	Classification	Source
Cyclopentene	205-532-9	142-29-0	Flam. Liq. 2 Acute Tox. 4 Asp. Tox. 1 Acute Tox. 4 Skin Irrit. 2	REACH registration C&L

https://echa.europa.eu/es/information-on-chemicals/cl-inventory-database/-/discli/details/1180

As you can see in the notifications summary:

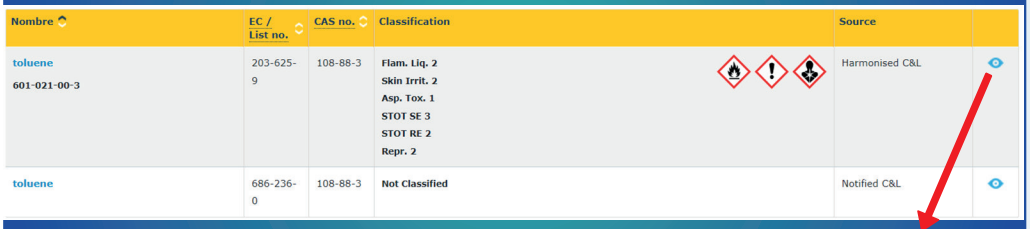
- There are12 different classifications proposed.
- The classification listed in the catalog is the one that received the highest number of notifications (64) and is as follows:
  - » Flammable liquids, category 2.
  - » Acute toxicity (via oral route), category 4.
  - » Aspiration hazard, category 1.
  - » Acute toxicity (cutaneous route), category 4.
  - » Skin corrosion/irritation, category 2.
- Considering all the proposed classifications, specific attention should be paid to the data included in the ECHA-REACH databases (paragraph 4.5.1), for the following hazard classes:

- » Flammable liquids.
- » Acute toxicity.
- » Skin corrosion/irritation.
- » Serious eye injuries/ ocular irritation.
- » Specific target organ toxicity - single exposure
- » Aspiration hazard.
- » Chronic hazard to the aquatic environment.

"Harmonized C&L" Substances These are substances notified, registered and evaluated under ECHA. The classification listed in the inventory is the result of this evaluation, and as it constitutes the official EU classification, it is therefore mandatory.

For these substances, the summary of notifications and the public data supporting the classification are also available (access to said data will be discussed in paragraph 4.5.1).

For example:
Substance: toluene (CAS 108-88-3)
From the ECHA-C&L catalog:



Nombre	EC / List no.	CAS no.	Classification	Source
toluene 601-021-00-3	203-625-9	108-88-3	Flam. Liq. 2 Skin Irrit. 2 Asp. Tox. 1 STOT SE 3 STOT RE 2 Repr. 2	Harmonised C&L
toluene	686-236-0	108-88-3	Not Classified	Notified C&L

https://echa.europa.eu/es/information-on-chemicals/cl-inventory-database/-/discli/details/30426

As can be seen, the catalog includes two entries. When this is the case, it is not necessary to consult all entries, it is sufficient to consult the first entry, as this will always be the most recent one and the one with the highest status in REACH ("Source" column).

As you can see in the catalog and in the summary of notifications:

- The official EU classification for toluene is:
  - » Flammable liquids, category 2.
  - » Skin corrosion/irritation, category 2.
  - » Aspiration hazard, category 1.
  - » Specific target organ toxicity - single exposure, category 3 (narcotic effects).

  - » Specific target organ toxicity - repeated exposure, category 1.
  - » Toxicity for reproduction, category 2.

- 157 different classifications are proposed. However, in this case, the official classification is not the one with the highest number of notifications. The official classification was proposed at 134 notifications and there are other proposed classifications with a higher number of notifications (there are proposed classifications with 2120, 1672 and 1302 notifications, for example).
- It is important to mention that, if the purpose of the search is the official EU classification of the substance, it is not necessary to access the summary of notifications, as the classification is in the catalog.
- However, if the purpose of the search is to obtain as much information as possible for a classification process of your own, you should consult the notifications summary and find out which hazard classes have been notified but not included in the official classification. Particular attention should be paid to obtaining data related to these other hazard classes.

4.4.2 NITE-J (Japan)

NITE-J[21] is a Japanese government reference database, created in 2006, which contains information for more than 5,500 chemicals, including the results of the GHS classification. These classifications are intended to be used as a reference by industry, but they are not mandatory.

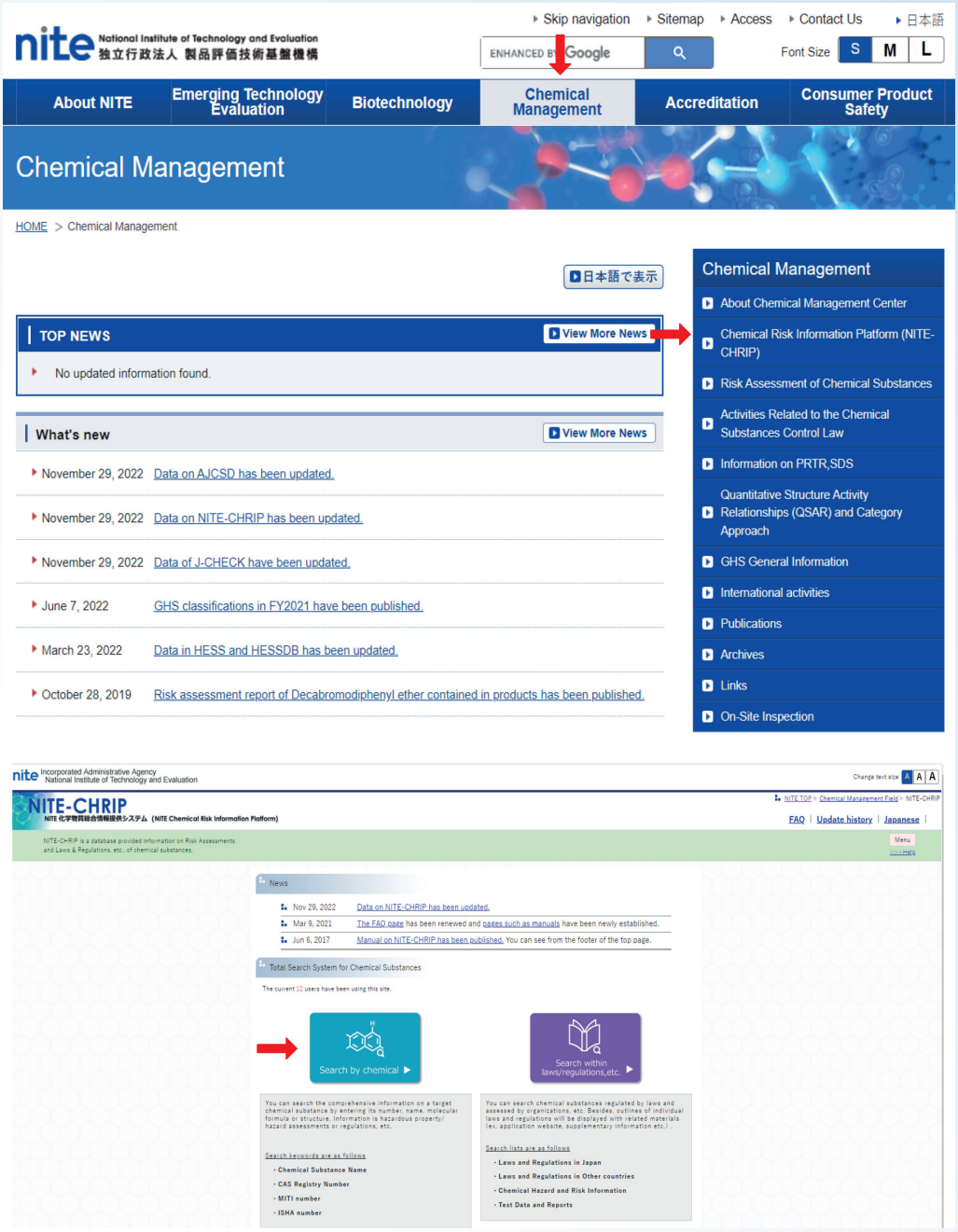
It is important to mention that, unlike the EU, Japan considers all GHS hazard classes and categories included in the 6th edition of the "purple book".

The database can be accessed in two different ways:

- Directly through the link at the footer of the page.
- Through the following route (Figure 3):
  - » Main page of NITE: https://www.nite.go.jp/en/chem/index.html
  - » "Chemical Management" tab.
  - » "Chemical Risk Information Platform (NITE – CHRIP)"
  - » "Search by chemical".

21 Available at: https://www.nite.go.jp/en/chem/chrip/chrip_search/srhInput

Figure 3.

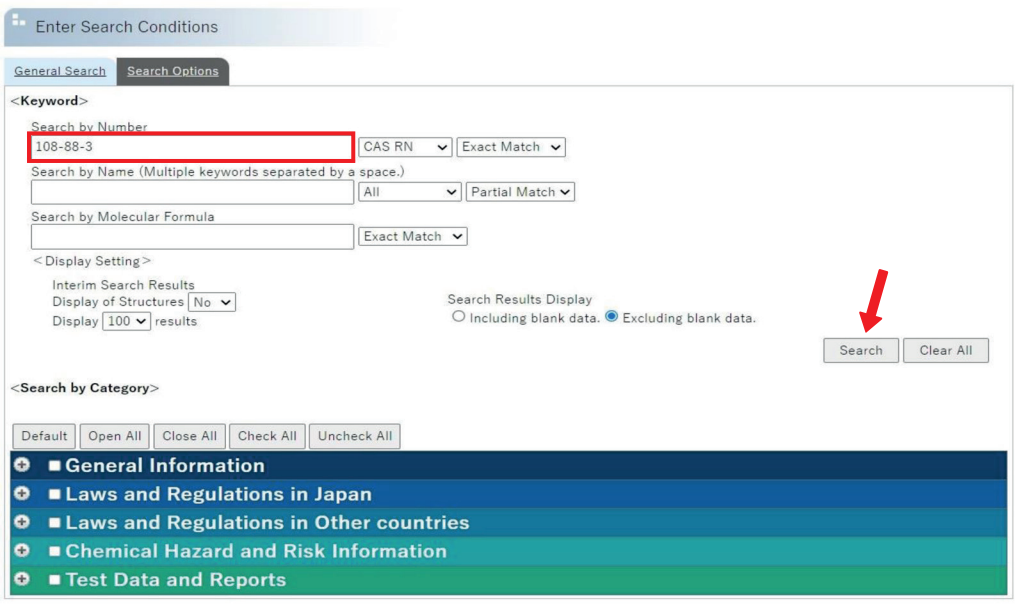


Search fields can be found on the main web page of the database:

- **By number (by default, CAS number).**
- **By name.**
- **By molecular formula.**

An example of a search for toluene (CAS 108-88-3) is presented in Figure 4.

Figure 4.



If the substance of interest is found in the database, a new window opens with a report containing the following sections:

- General information.
- Laws and regulations in Japan.
- Laws and regulations in other countries.
- Information on the hazards and risks of chemical substances.
- Testing data and reports.

In the section called general information, you must confirm that the substance is the substance of interest.

The classification results can be found in the "Chemical Hazard and Risk Information" section, particularly in the first subsection ("GHS Classification Results"), where all the results obtained and the year are listed. This subsection contains all the results obtained and the year. The most reliable classification is the most recent one.

In all cases, the classifications are available as tables in two formats:

- Web, the result is displayed on the actual website.
- Excel, the file is automatically downloaded.

In both formats, physical, human health and environmental hazards are included in three different tables, containing the following information:

- Class of hazard.
- Category of hazard.
- Pictogram of hazard.
- Signal word.
- Indication of hazard.
- Cautionary advice.
- Justification for the classification.

There are three differences between the two formats:

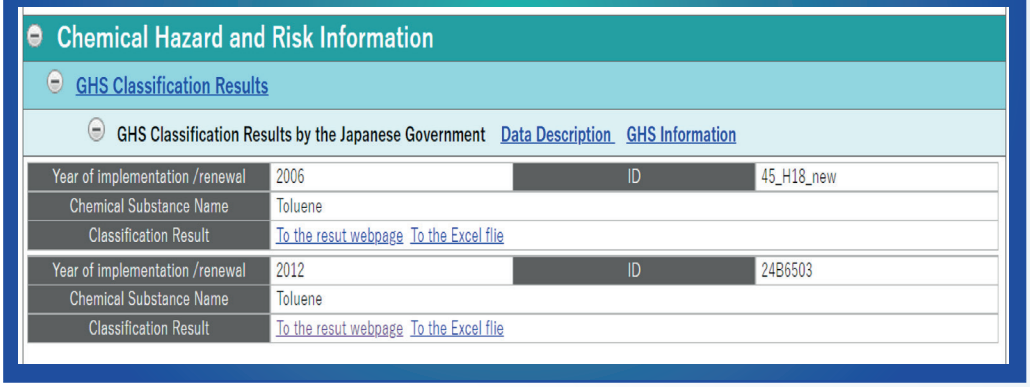
- In the Web format, general information and the references used are included.
- In the Web format, the hazard pictograms are shown with the image and in the Excel file with the name that identifies it.
- In the Web format, the hazard pictogram and the signal word are included in the same column, while in the Excel file, these are in two different columns.

For example:

Substance: toluene (CAS 108-88-3)

Link to the report for toluene

The following information appears in the section "Chemical Hazard and Risk Information":



Chemical Hazard and Risk Information

GHS Classification Results

GHS Classification Results by the Japanese Government Data Description GHS Information

Year of implementation /renewal	2006	ID	45_H18_new
Chemical Substance Name	Toluene		
Classification Result	To the resut webpage To the Excel file		
Year of implementation /renewal	2012	ID	24B6503
Chemical Substance Name	Toluene		
Classification Result	To the resut webpage To the Excel file		

According to this information, there are two suggested classifications for toluene, the first one made in 2006 and the last one in 2012.

The following links provide access to the result of the classification performed in 2012, both in Web and Excel format.

- Classification of toluene in Web format
- Classification of toluene in Excel format

The suggested classification of toluene by the Japanese government is:

- Flammable liquids, category 2.
- Acute toxicity (inhalation: vapors), category 4.
- Skin corrosion/irritation, category 2.
- Serious eye injuries/ ocular irritation, category 2B.
- Reproductive toxicity, category 1A; effects on or via lactation.
- Specific target organ toxicity - single exposure, category 1.
- (central nervous system)
- Specific target organ toxicity - single exposure, category 3
- (irritation of the respiratory tracts).
- Specific target organ toxicity - single exposure, category 3
- (narcotic effects).
- Specific target organ toxicity - repeated exposures, category 1 (central nervous system, kidney).
- Aspiration hazard, category 1.
- Hazards to the aquatic environment (acute), category 2.
- Hazards to the aquatic environment (chronic), category 3.

4.4.3 HSNO CCID (New Zealand)

HSNO CCID[22] is a database of chemicals classified by the New Zealand Environmental Protection Authority, according to the current regulations that were updated in 2021.

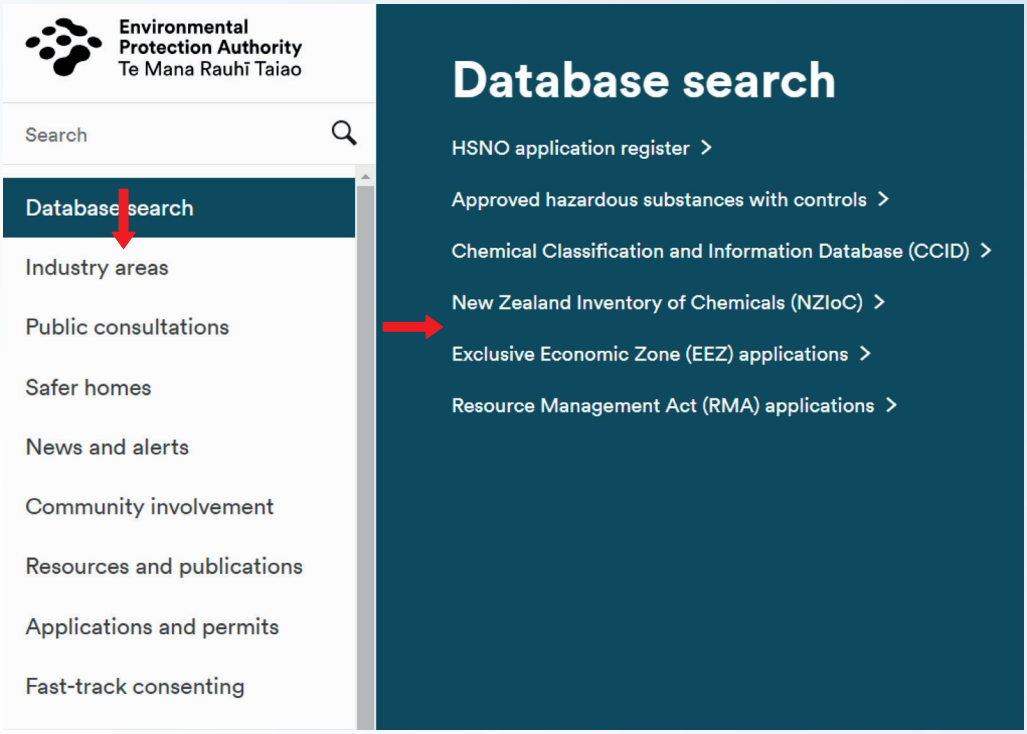
These regulations are based on the 7th revised edition of the "purple book" and include all GHS hazard classes and categories. In addition, for pesticides, terrestrial ecotoxicity hazards not covered by the GHS are included.

The database contains the GHS classifications, some physical property data, and a summary of the data on which the classification is based for 5,436 chemicals. As they are based on regulation and made by a state agency, the classifications in this database are mandatory in New Zealand. Access to the database can be carried out in two different ways:

22 Available at: https://www.epa.govt.nz/database-search/chemical-classification-and-information-database-ccid/

- Directly through the link at the footer of the page.
- Through the following route (Figure 5):
  - » Main page of the EPA of New Zealand: https://www.epa.govt.nz/
  - » "Database Search" → "Chemical Classification and Information Database (CCID)"

Figure 5.



The search can be performed either by the CAS number or by the name of the chemical.

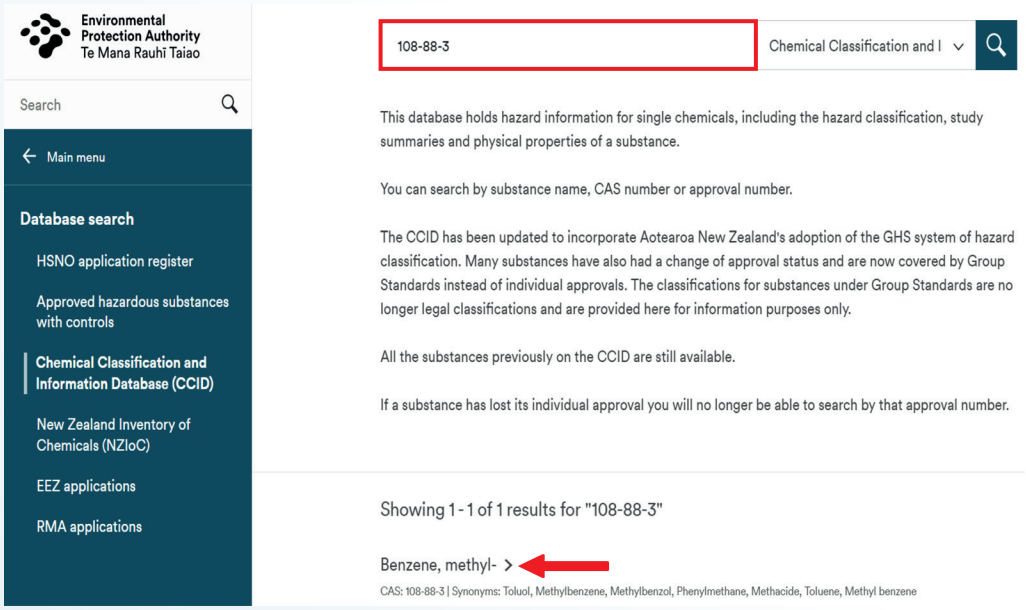
An example of a search result for toluene (CAS 108-88-3) is presented in Figure 6.

In some cases, the search may return more than one result for the same substance, if the substance may be in a different physical state or with different purity.

If the substance of interest is found in the database, by clicking on the substance name, a new window opens with a report containing the following sections:

- Data on the substance.
- The GHS hazard classes and categories in which the substance was classified.

Figure 6

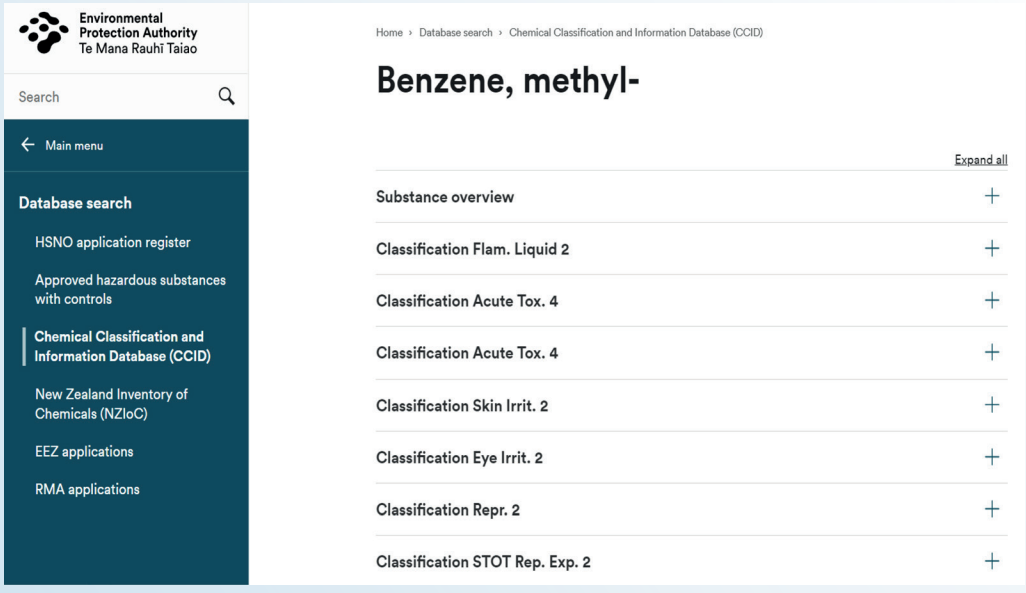


For each class and category, the data justifying the classification is included. In the case of acute toxicity, the classification according to the route of exposure (ingestion, cutaneous, inhalation) is indicated separately.

Example:

Substance: toluene (CAS 108-88-3)

Link to the report for toluene



In this case, it is noted that the classification acute toxicity, category 4, is repeated. If you expand on each of the classifications (by clicking on +), you can see that in the first case, it refers to the ingestion route (oral) and, in the second case, to the inhalation route of vapors.

The classification of toluene suggested by the government of New Zealand is:

- Flammable liquids, category 2.
- Acute toxicity (ingestion), category 4.
- Acute toxicity (inhalation: vapors), category 4.
- Skin corrosion/irritation, category 2.
- Serious eye injuries/ ocular irritation, category 2.
- Toxicity for reproduction, category 2.
- Specific target organ toxicity - repeated exposure, category 2.

4.4.4.Use of the GHS classification databases

The GHS classification databases can be useful for:

1. Complying with the regulation.
2. Guiding the search for data.

Each of the above points will be explained below.

1. Complying with the regulation.

Since EU and New Zealand classifications are mandatory, a producer that must export a chemical to these locations must adopt these official classifications and need not undertake a classification process of its own.

2. Guiding the search for data.

The analysis of the different classifications allows us to guide the search for data, prioritizing the search for data that supports the three classifications and continuing with the search for the other data.

When comparing the different classifications, three different situations can be distinguished:

a. Complete positive match: match in hazard class and category in all three classifications.

b. Partial match or overlap:
   - There is an overlap in hazard class and category in two of the three classifications.

- There is an overlap in class, but not in hazard category.
- There is a hazard class listed in only one of the classifications.

c. Complete negative match: hazard classes not included in any of the three classifications.

It is important to note that, unfortunately, situation b) is the most frequent one. This can be due to factors such as:

- **The modular approach.**

  The modular approach (paragraph 1.1.3.1.5 of the "purple book") allows countries to choose which hazard classes and categories to apply in their regulations.

  For example, the EU did not adopt category 4 for flammable liquids. Therefore, a substance classified as a flammable liquid, category 4 in the NITE-J and/or HSNO CCID databases, will never appear in the ECHA C&L catalog.

  The modular approach applied by the EU, through REACH, is included in the Annex.

- **The judgment of the experts involved in the process for each of the classifications.**

  For example, the same data can be evaluated as reliable by one expert and not reliable by another. Even the same data considered reliable by two experts can be interpreted in such a way that one leads to a certain classification and the other to a different classification.

From the above, it is possible to conclude:

- As of today, a globally harmonized system is available, but globally harmonized classifications are not yet available.
- Expert judgment is a critical aspect that affects the outcome of a classification.

According to the results of the analysis of the three classifications, the search for data can be oriented according to the following prioritization criteria:

1. Data for the hazard classes of situation a) (complete positive match).

   In principle, reliable data justifying these classifications should be found. If not, expert judgment or a decision to carry out the corresponding test may be necessary (see paragraph 3.4).

2. Data for the hazard classes of situation b) (partial overlap.

   Reliable data should be found for these hazard classes, but expert judgement will be required to decide on differences in classifications.

3. Data for the hazard classes of situation c) (complete negative match).

   It is possible that no data will be found. If data is found, expert judgment is probably required to at least assess their quality.

Remember that there are two possible outcomes in carrying out the classification process for each GHS hazard class: classifiable or not classifiable. In either case, such classification must be justified on the basis of reliable data.

For example, the classification of a chemical **as non-hazardous** must be justified on the basis of reliable data (requires the search for reliable data).

The following is an example of how GHS classification databases can be used to guide the search for data.

For example:

Substance: toluene, CAS 108-88-3 (same substance used in previous examples).

ECHA C&L Classification

- Flammable liquids, category 2.
- Skin corrosion/irritation, category 2.
- Aspiration hazard, category 1.
- Specific target organ toxicity - single exposure, category 3 (narcotic effects).
- Specific target organ toxicity - repeated exposure, category 1.
- Toxicity for reproduction, category 2.

NITE-J Classification

- Flammable liquids, category 2.
- Acute toxicity (inhalation: vapors), category 4.
- Skin corrosion/irritation, category 2.
- Serious eye injuries/ ocular irritation, category 2B.
- Reproductive toxicity, category 1A; effects on or via lactation.
- Specific target organ toxicity - single exposure, category 1 (central nervous system).
- Specific target organ toxicity - single exposure, category 3 (respiratory tract irritation).
- Specific target organ toxicity - single exposure, category 3 (narcotic effects).
- Specific target organ toxicity - repeated exposures, category 1 (central nervous system, kidney).
- Aspiration hazard, category 1.
- Hazards to the aquatic environment (acute), category 2.
- Hazards to the aquatic environment (chronic), category 3.

HSNO CCID Classification

- Flammable liquids, category 2.
- Acute toxicity (ingestion), category 4.
- Acute toxicity (inhalation: vapors), category 4.
- Skin corrosion/irritation, category 2.
- Serious eye injuries/ ocular irritation, category 2.
- Toxicity for reproduction, category 2.
- Specific target organ toxicity - repeated exposure, category 2.

From the analysis of the different classifications, it is possible to establish the following prioritization of the search for relevant data for toluene:

Priority 1 (complete positive match)

- Flammable liquids, category 2.
- Skin corrosion/irritation, category 2.

Priority 2 (partial match)

- Acute toxicity (ingestion).
- Acute toxicity (inhalation).
- Serious eye injuries/ ocular irritation.
- Toxic for reproduction.
- Specific target organ toxicity - single exposure.
- Specific target organ toxicity - repeated exposure.
- Aspiration hazard.
- Hazards to the aquatic environment (acute).
- Hazards to the aquatic environment (chronic).

Priority 3 (complete negative match)

- Acute toxicity (cutaneous).
- Respiratory or cutaneous sensitivity.
- Germ cell mutagenicity.
- Carcinogenicity.

4.5 Databases of properties of chemical substances

The ranking or classification process always requires obtaining reliable data, which poses at least two challenges:

1. **Obtaining data.**
2. **Determining the reliability of the data obtained, according to what is established in paragraph 2.4.2.**

There are many databases that can be used to obtain relevant data. Depending on the information they provide, these databases can be divided into three types:

a. Only the data is reported, but not its reliability, and not enough information is provided to determine its reliability (only the reference of the data, which is generally not available). For example, GESTIS, NITE-J and HSNO CCID.

b. The data is reported, not its reliability, but information is provided to determine its reliability. For example: IARC.

c. The data and reliability is reported, and information is provided that allows us to confirm or negate the reported reliability. For example, ECHA – REACH.

According to the above, type a) databases are not useful for the purposes of the classification process. Likewise, type b) and c) databases require the judgment of experts to determine the reliability of a piece of data, in the event that the evaluation performed by the source itself presents an ambiguous result or leaves doubts as to the origin of the data.

In any case and, ultimately, it is always our responsibility to decide on the reliability of data.

The ECHA - REACH and IARC databases are presented in detail below.

4.5.1 ECHA – REACH

ECHA - REACH[23] is a database, within the ECHA portal, that compiles all data that were taken into account for the registration of about 25,000 substances, according to Regulation (EC) 1907/2006 (REACH).

Access to the database can be carried out in two different ways:

- Directly through the link at the footer of the page.
- Through the following route (Figure 7):
  - » Main page of the ECHA: https://echa.europa.eu/es/home.
  - » "Chemical Information" tab.
  - » "REACH" → "Registered substances".

The database search engine allows us to search by substance name, CAS number or other identifying numbers, as presented in Figure 8, where toluene is taken as an example.

If the substance is found in the database (only substances identified as "Harmonized C&L" by ECHA), all existing registration entries for that substance are opened, as presented in Figure 9.

23 Available at: https://echa.europa.eu/es/information-on-chemicals/registered-substances

Figure 7.

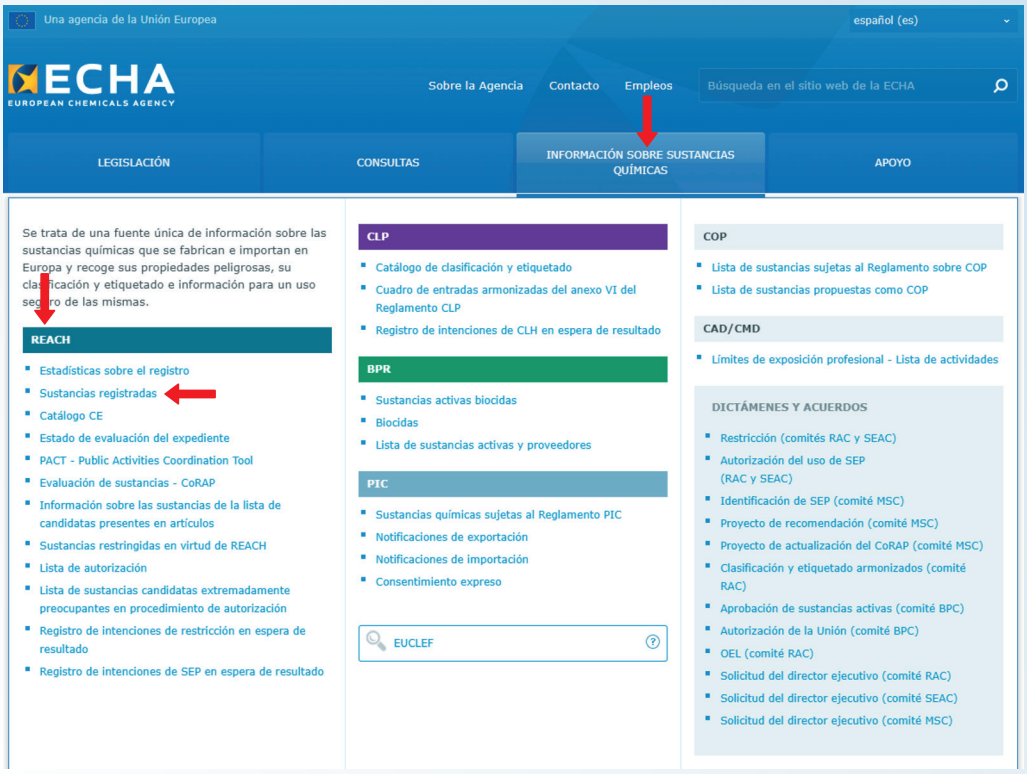


Figure 8.

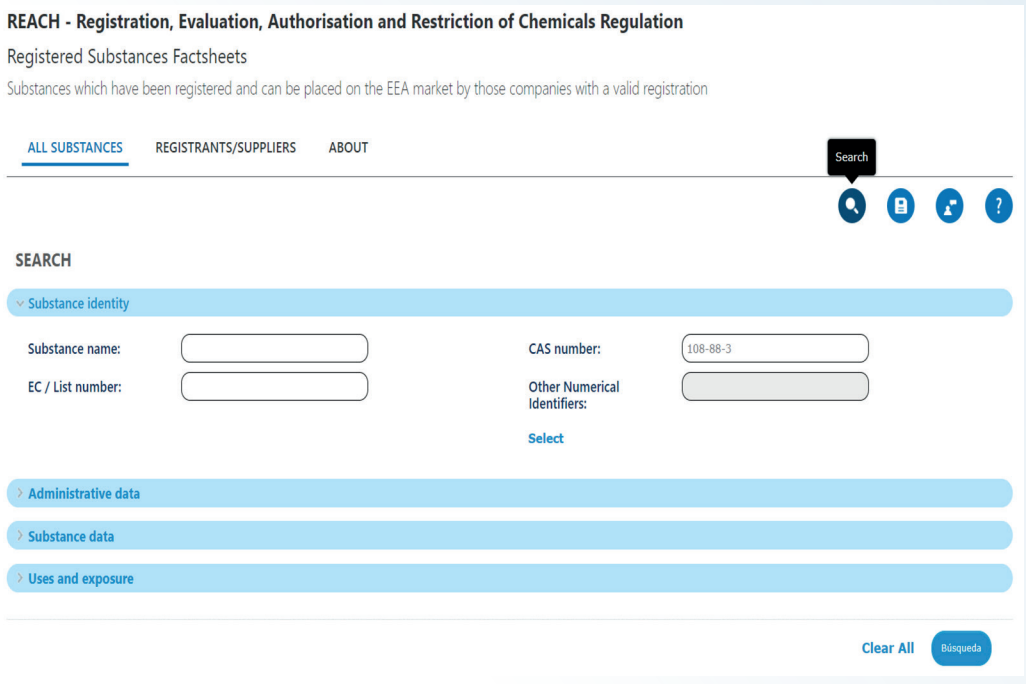


Figure 9.

Name	EC / List no.	CAS no.	Registration Status	Registration type	Submission type	Total tonnage band	Last Updated	Details
Toluene	203-625-9	108-88-3	Active	Full		≥ 1 000 000 to < 10 000 000 tonnes	05-08-2022	
Toluene	203-625-9	108-88-3	Cease Manufacture	Intermediate		Cease manufacture	15-04-2018	

The search results are presented in table format (one row for each record), with the following columns:

- Name.
- CE/List (EU identifying number).
- CAS.
- State of registration:
  - » "Active":the substance is marketed in the EU.
  - » "Cease manufacture": the substance is no longer marketed, but the registration is still considered valid.
  - » "No longer valid": the registration of the substance is not considered valid
- Type of registration:
  - » "Full": full registration
  - » "Intermediate": intermediate registration.
  - » "NONS notification": notification of a new substance.
- Type of shipment:
  - » Individual.
  - » Combined.
- Range of tons manufactured.
- Last update (date of last update).
- Details (👁)

  By clicking on the symbol, we can access the dossier with data on the substance.

The largest amount of data is found in the last update of the active and complete records.

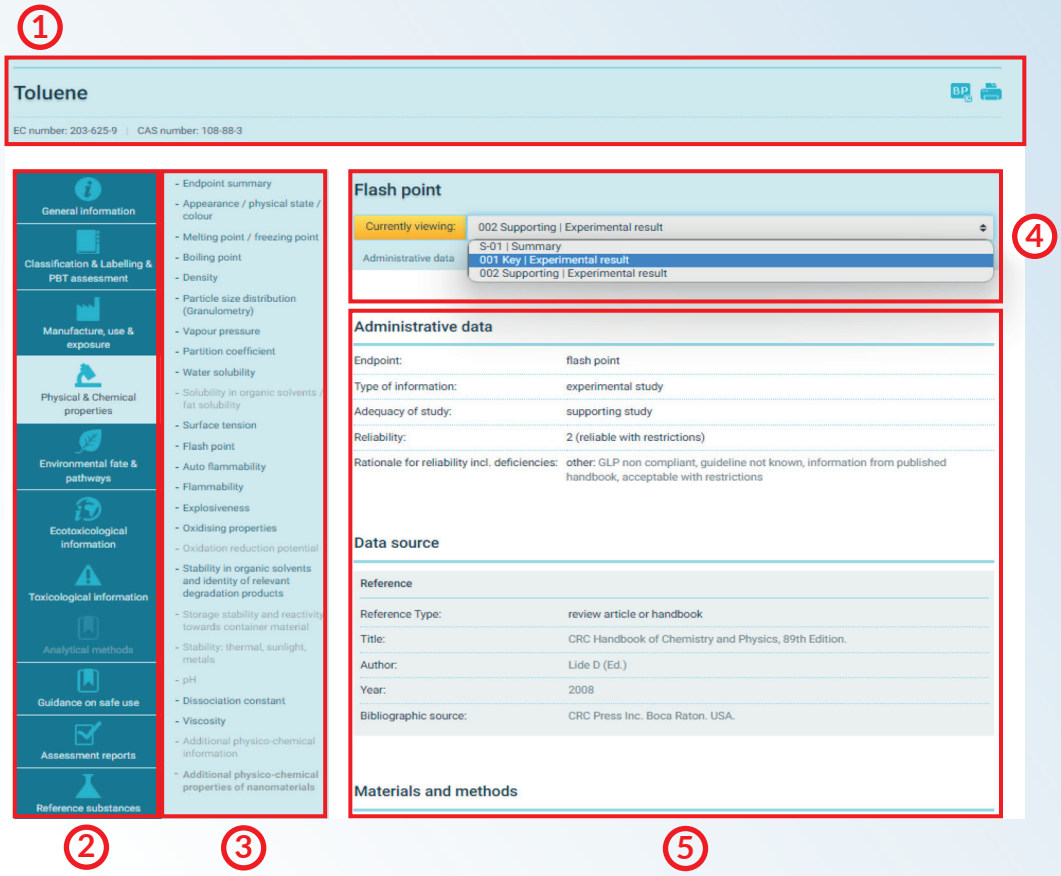
By clicking on the symbol 👁 of the corresponding record, we can access the file of the substance.

The files can be divided into five parts (Figure 6):

1. Header, in which the name and the CE and CAS numbers of the substance are provided.
2. Main menu, on the left-hand side of the page.
3. Secondary menu, on the left-hand side of the page and to the right of the main menu.
4. Data identification ("Currently viewing"), in the central section.
5. Data information, in the central section.

For example, Figure 10 shows the toluene dossier.

Figure 10.



The sections of the main menu that are of interest for the data search are as follows:

- "Physical & Chemical properties".
- "Environmental fate & pathways".
- "Ecotoxicological information".
- "Toxicological information".

Subsections of the secondary menu consist of the properties related to the main menu section. For example, the submenu of the main menu physical and chemical properties contains boiling point, flash point, partition coefficient, water solubility, among others.

The search for data within the dossier of the substance of interest is performed as follows:

1. Click on the corresponding section of the main menu ("Physical & Chemical properties" in the example in Figure 6).

2. Click on the property of interest ("Flash point" in the example in Figure 6).
3. Click on the data ID and a new menu with all available data is displayed. In the example in Figure 6, the following three pieces of data were displayed:

   - S-01 | Summary.
   - 001 Key | Experimental Result.
   - 002 Supporting | Experimental Result.

   Each piece of data includes the categorization of the data according to the ECHA criteria mentioned in paragraph 2.4.3 of these guidelines ("Key", in the example selected from Figure 6) and the type of data ("Experimental Result", in the example selected from Figure 6).

4. The data of interest is selected (for example, "001 Key | Experimental Result", in Figure 6).

With the exception of the "Summary" data, the reliability assigned by ECHA, according to the criteria presented in paragraph 2.4.2, is included for all other data.

In the example in Figure 6: Reliability: 2 (reliable with restrictions).

In principle, the reliability assigned by ECHA can be taken as good, but in any case, it is possible to review (and modify) it.

The data information includes the following sections:

- Administrative data.
- Data source.
- Materials and methods.
- Results and discussion.
- Applicant´s summary and conclusion.

There are two objectives that can be met by using this database:

1. To obtain data to support the classification made by ECHA. In this case, only data categorized as "Key" needs to be consulted.
2. Obtain data to support our own classification. In this case, we need to consult all data categorized with reliability 1 (reliable without restrictions) and 2 (reliable with restrictions).

For example:

Substance: toluene (CAS 108-88-3)
Property: flash point.
Data: "001 Key | Experimental Result"

Link to the data

Most relevant information on the data:

Administrative data:
- Experimental study.
- Key study.
- Reliability 2 (reliable with restrictions).

Data source:
- Merck Index, 2006 (handbook).

Materials and methods:
- Vessel or closed crucible assay (meets GHS requirement).
- No information on whether the test was performed according to OECD good practices.
- Material tested: toluene (purity not specified).

Results and discussion:
- Flash point: 4.4ºC to 1013 hPa of pressure.

Summary and conclusion of the record:
- The flash point of toluene is 4.4ºC.

This partly justifies the classification of toluene as flammable liquid category 2 (flash point < 23ºC).

A reliable boiling point of > 35ºC should be obtained to confirm the classification.

4.5.2 IARC

The International Agency for Research on Cancer (IARC) is an autonomous agency of the United Nations World Health Organization created in 1965. IARC has 27 participating states as of the date of publication of this document.

IARC conducts quality independent research that is highly respected by researchers, governments and the general public.

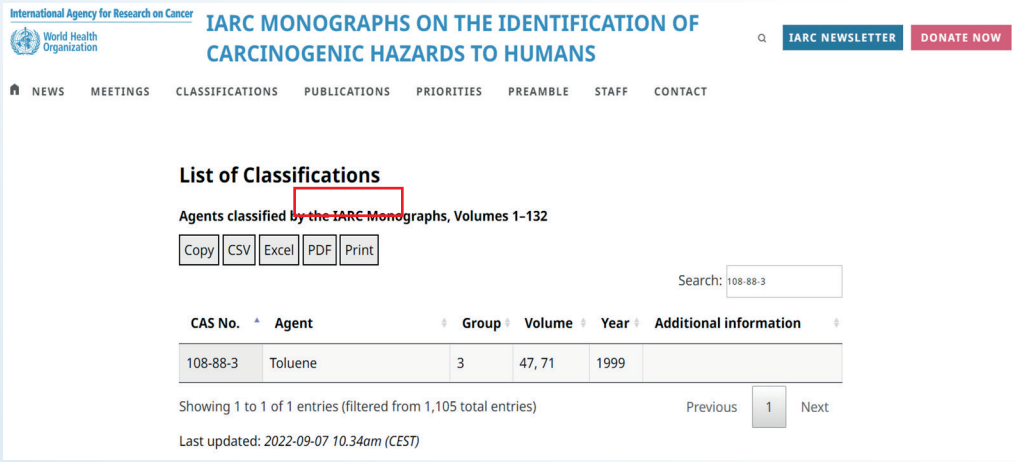
As a result of this research, IARC produces and disseminates assessments, which are reliable references due to their interdependence. For this reason, it is possible to assign them reliability 1 (reliable without restrictions).

The reference assessments can be found in the agent classification list and the monographs on identification of carcinogenic hazards to humans.

Both documents can be found on the IARC web page "IARC Monographs on the Identification of Carcinogenic Hazards to Humans"[24]. The classification list has a search engine that includes 1,105 entries, is presented in table format, available on the Web or downloadable in Excel and PDF formats.

Figure 11 presents the search result for toluene (CAS 108-88-3).

Figure 11.



The search for an agent can be performed by name or CAS number. An agent can be an individual substance or a family of substances. For example, potassium dichromate (CAS 7778-50-9) is not listed in the search engine because its evaluation is part of the chromium VI family of compounds (CAS 18540-29-9, corresponding to the Cr^{6+} ion).

If the agent of interest is found in the classification list, the following information is displayed (Figure 11):

- **Group:** refers to the classification group assigned according to the IARC criteria, as will be seen below.
- **Volume**: all IARC monographs and supplements that include evaluations of the agent are indicated. For monographs, the volume number is simply provided and supplements are identified by prefixing the publication number with the prefix Sup.

24 Available at: https://monographs.iarc.who.int/list-of-classifications

- **Year:** the year of the most recent monograph or supplement is provided.

The IARC classifies carcinogens according to human, animal and mechanistic evidence.

The human and animal evidence is divided into four categories:

- Sufficient.
- Limited.
- Inadequate.
- The evidence suggests lack of carcinogenicity.

On the other hand, mechanistic evidence is divided into three categories:

- Strong:
  - » Based on the mechanistic class.
  - » Key characteristics.
  - » The mechanism is not relevant for humans.
- Limited.
- Inadequate.

In line with this evidence, IARC classifies carcinogens into four groups, as presented in Table 6.

Table 6.

Evidence of cancer in humans	Evidence of cancer in animals	Mechanistic evidence	Evaluation
Sufficient			Carcinogenic (Group 1)
	Sufficient	Strong (based on the humans exposed)	
Limited	Sufficient		Probably carcinogenic (Group 2A)
Limited		Strong	
	Sufficient	Strong (based on human cells or tissue)	
		Strong (based on mechanistic class)	
Limited			Possibly carcinogenic (Group 2B)
	Sufficient		
		Strong (on the basis of experimental systems)	
	Sufficient	Strong (does not work in humans)	Not classifiable (Group 3)
Any other situation not listed above			

The criteria for classification of carcinogens in the GHS are consistent with those of the IARC; the interpretation of the terms is sufficient, and is limited.

In accordance with the GHS, carcinogenic chemicals are classified into the following three categories:

- **Category 1A**. Substances known to be carcinogenic to man, based on the existence of data in human studies.
- Sufficient evidence in humans is necessary to assign this hazard category.
- **Category 1B.** Substances presumed to be carcinogenic to man, based on the existence of data in animal studies.
- Sufficient evidence in animals is necessary to assign this hazard category.
- **Category 2.** Substances suspected of being carcinogenic to man.
- Limited evidence in humans and/or animals is necessary to assign this hazard category.

Table 7 shows the correspondence between the IARC groups and the GHS hazard categories.

Table 7.

Evidence in humans	Evidence in animals	Mechanistic evidence	IARC Group	GHS Category
Sufficient			Group 1	1A
	Sufficient	Strong (based on the humans exposed)		1B
Limited	Sufficient		Group 2A.	1B
Limited		Strong		2
	Sufficient	Strong (based on human cells or tissue)		1B
		Strong (based on mechanistic class)		To be assessed by experts
Limited			Group 2B	2
	Sufficient			1B
		Strong (on the basis of experimental systems)		To be assessed by experts
	Sufficient	Strong (does not work in humans)	Group 3.	Classifiable or not classifiable.
Any other situation not listed above				

In line with Table 7, it is not possible to extrapolate directly between the IARC group and the GHS hazard category, except for group 3 agents, which will not be classified in the GHS.

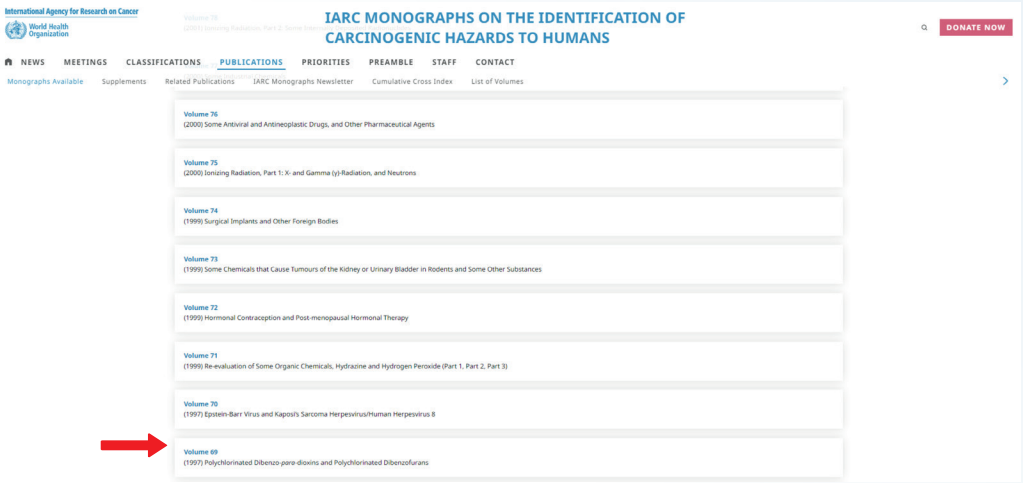
In order to classify a substance according to the GHS from an IARC classification, it is necessary to know the evidence on which the classification was based. Such information can be found in the IARC monographs and supplements, which are available by clicking on "Publications" (see Figure 7).

The "Publications" web page [25] lists all IARC publication types, including monographs and supplements, sorted by decreasing volume number (the first document in the list is the latest volume and, at the same time, the most recent).

The following figures show the sequence to follow to find the desired monograph or supplement. The monograph volume 71 of 1999, which contains the evaluation of toluene, will be used as an example.

Figure 12.

Figure 13.



25 Available at: https://monographs.iarc.who.int/cards_page/publications-monographs/

Figure 14.

You need to click on the table of contents to locate the section of the monograph corresponding to the substance of interest and also on the corrigenda, to verify if the monograph has not undergone any corrections that may be relevant.

By clicking on the name of the desired substance, you automatically download a pdf file with the corresponding part of the monograph.

The monographs of a substance have the following sections:

- Exposure data.
- Cancer studies in humans.
- Cancer studies in humans.
- Other data relevant to a carcinogenicity assessment and its mechanisms.
- Summary of reported data and evaluation.
- References.

Figure 15.

ABOUT THIS BOOK | TABLE OF CONTENTS | CORRIGENDA

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Contents and Note to the Reader
List of Participants
Preamble
General Remarks
Summary of Final Evaluations
Cumulative Cross Index to *IARC Monographs*

THE MONOGRAPHS

Part One: Compounds reviewed in plenary sessions (comprehensive monographs)

Acrylonitrile

1,3-Butadiene [superseded by Volume 97]

Chloroprene

Dichloromethane

Part Two: Other compounds reviewed in plenary sessions

Acetaldehyde [see also Volume 96]
Aziridine
Benzoyl peroxide
n-Butyl acrylate
γ-Butyrolactone
Caprolactam
Carbon tetrachloride
Catechol
α-chlorinated toluenes and benzoyl chloride
1,2-Dibromo-3-chloropropane
1,2-Dichloroethane
Dimethylcarbamoyl chloride
Dimethylformamide
Dimethyl sulfate
1,4-Dioxane
Epichlorohydrin
1,2-Epoxybutane
Ethylene dibromide (1,2-dibromoethane)
Hydrogen peroxide
Hydroquinone
Methyl bromide
Methyl chloride
Phenol
Polychlorophenols and their sodium salts [see also Volume 117]
1,1,2,2-Tetrachloroethane
Toluene
Toluene diisocyanates

In principle, it is sufficient to read section 5, but ideally or in case of doubt you should read the entire monograph (some of them consist of hundreds of pages and are available only in English).

To classify a substance as carcinogenic according to the GHS, based on an IARC classification, the following procedure is suggested:

1. Enter the web page "IARC Monographs on the Identification of Carcinogenic Hazards to Humans" and enter the CAS number or a name identifying a family (in English) in the IARC search engine (Figure 7).
2. If the substance is listed, note all publications associated with that substance, both monographs and supplements (Figure 7).
3. Click on "Publications" and download the most recent publication listed (Figures 8, 9, 10 and 11).
4. Read section 5 of the monograph and, if necessary, other sections of the monograph.
5. If this monograph is not sufficient to perform the classification, download the next most recent publication and repeat the process until the information needed to classify is obtained.
6. With the IARC assessment, classify the product according to the GHS using Table 7 as a reference.

For example:

Substance: toluene (CAS 108-88-3)

<u>From the list of classifications:</u>

- Classification: group 3 → According to Table 7: Not classified in the GHS.
- Two publications: monographs volume 47 and 71 (year 1999).

Link to toluene monograph in volume 71

<u>From section 5 (evaluation)</u>:

- Inadequate evidence in humans.
- Evidence suggests the absence of carcinogenicity in animals.

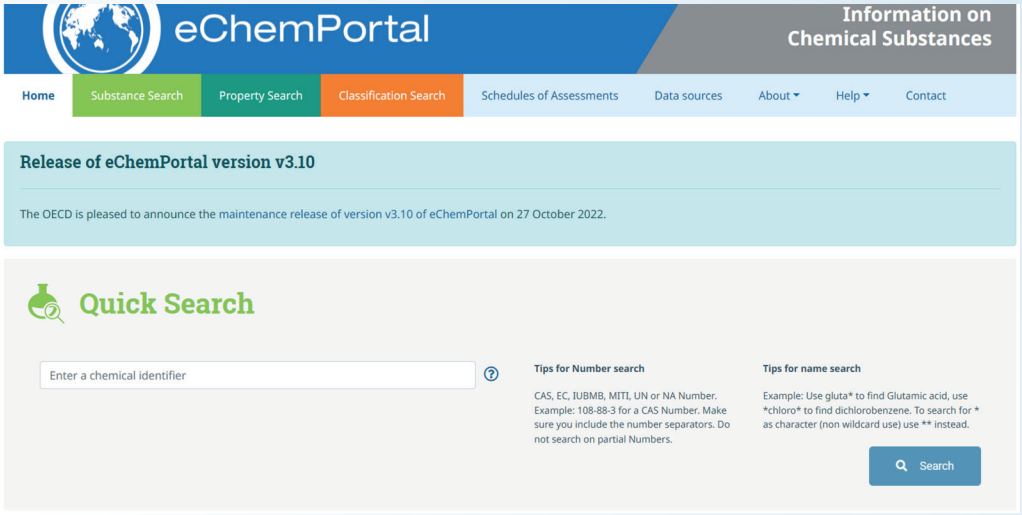
Confirmed not to warrant classification in any of the GHS categories.

4.6 eChemPortal (OECD)

The eChemPortal[26] is an OECD effort with input from governments and other stakeholders and developed in collaboration with ECHA. The eChemPortal provides free public access to 35 databases with information on properties and classification results according to the GHS of chemicals.

The home page of this portal can be seen in Figure 16.

Figure 16.



From this page, all databases containing information on the substance of interest can be accessed in the search engine (with CAS number, English name or other substance identifier).

If you only want to search for properties, click on "Property Seach" and enter the CAS number, English name or other substance identifier in the search engine.

If you only want to search for GHS classifications, click on "Classification Seach" and proceed in the same way as in the previous paragraph.

The following is an explanation of how the following databases seen above are identified in the eChemPortal:

ECHA C&L → ECHA C&L inventory.
NITE – J → GHS-J.
HSNO CCID → HSNO CCID.
ECHA REACH → ECHA REACH.

26 Available at: http://www.echemportal.org/echemportal/

When a search returns more than one result from the same database, all of them should be queried to determine which is the most recent or useful.

The eChemPortal is an excellent resource for:

- Having GHS data and classifications in one place.
- Consulting databases other than those studied in these guidelines.

**“This is not the final version of this document.
The final version will be ready in September 2023;
nevertheless, the contents of the guidance will be the same”.**

5. CASE STUDIES

Three case studies for the following substances are presented below:

- **Potassium dichromate**
  CAS 7778-50-9
  Solid substance
- **Di-isononyl phthalate**
  CAS 28553-12-0
  Liquid substance
- **Ethylene oxide**
  CAS 75-21-8
  Gaseous substance

Each case study will be solved considering different purposes:

- Complying with the regulation (paragraph 4.4.4).
  In this case, the EU regulation (REACH) for potassium dichromate.
- Guiding the search for data (paragraph 4.4.4).
  In this case, establish the data search prioritization for di-isononyl phthalate and obtain the data.
- Obtain data to support our own classification (paragraph 4.5.1).
  In this case, data for the classification of ethylene oxide.

Links to the following (as applicable) are included for each case study:

- The web pages of the databases seen above.
- The data that justifies the classification or the only available data (even if it does not justify the classification).

In the latter case, all the data should be analyzed one by one until at least one data that justifies the classification is found.

5.1 Case study No. 1 - Potassium dichromate (CAS 7778-50-9)

5.1.1 Resolution

For this case study, the purpose is to comply with regulations, in particular EU regulations (REACH), which implies carrying out two searches:

1. Official EU Classification in the ECHA C&L database.
2. Data which supports the classification, based on the ECHA-REACH database.

1. Official classification of the EU.

Link to the ECHA C&L web page

Research result for potassium dichromate - There is a single entry, with a registration status "Harmonized C&L", confirming that this is an official classification.

Classification:

- Oxidizing solids, category 2.
- Acute toxicity (oral), category 3.
- Acute toxicity (cutaneous), category 4.
- Skin corrosion/irritation, category 1B.
- Skin sensitivity, category 1.
- Acute toxicity (inhalation), category 2.
- Respiratory sensitivity, category 1.
- Germ cell mutagenicity, category 1B.
- Carcinogenicity, category 1B.
- Specific target organ toxicity - Repeated exposure, category 1.
- Hazards to the aquatic environment (acute), category 1.
- Hazards to the aquatic environment (chronic), category 1.
- Toxicity for reproduction, category 1B.

2. Data which supports the classification

Link to the ECHA C&L web page

Result of the search for potassium dichromate - There are two entries:

- Active/Full (12/15/2021)
- Active/Intermediate (10/ 31/2012)

Link to the complete ECHA - REACH potassium dichromate registration dossier

- Oxidizing properties

Link to the data

Expert judgment is required to interpret the entry or conduct the assay in accordance with the Manual of Tests and Criteria.

- Acute toxicity
  - » Oral route
    001 Key | Experimental result
  - » Cutaneous route
    002 Supporting | Read-across (Category)
  - » Via inhalation
    001 Key | Experimental result
- Corrosion/irritation
  - » Skin corrosion/irritation
    Observations related to human exposure (direct observations)
    001 Key | Read-across (Category)
- Sensitivity
  - » Cutaneous
    Observations related to human exposure
    (sensitization data in humans)
    001 Key | Read-across (Category)
  - » Respiratory
    Observations related to human exposure
    (sensitization data in humans)
    002 Key | Read-across (Category)
- Genetic toxicity
  - » In vivo
    002 Weight of evidence | Read-across (Category)
- Carcinogenicity
  S-01 Summary
  The data does not justify the classification. An expert judgment is required.

  IARC Assessment
  Classification: Group 1
  Monograph (Volume 100C, 2012): Sufficient evidence in humans and animals

According to this assessment, classification in GHS category 1A is justified.

However, since the purpose is to comply with an official regulation (REACH), the classification in ECHA category 1B cannot be changed.

- Toxicity by repeated doses
  - » Inhalation

    001 Weight of evidence | Read-across (Category)

- Hazards to the aquatic environment (acute), category 1.

  Data: Aquatic toxicity: short-term aquatic toxicity in invertebrates
  Link to the data

- Aquatic toxicity
  - » Long-term for aquatic invertebrates
    Link to the data
    The data does not justify the classification. Expert judgment or testing (ideally, according to one of the following OECD guidelines) is required: 201, 210 or 211).

- Toxicity for reproduction
  - » Developmental toxicity/teratogenicity
    002 Supporting | Experimental result

5.1.2 Conclusions

- In accordance with the official classification of the EU, potassium dichromate has 13 hazards:
  - » Physical hazards: 1.
  - » Health hazards: 10.
  - » Environmental hazards: 2.

- From the ECHA-REACH database:
  - » Data justifying the classification has been found for 10 hazard classes.
  - » For 2 classes of hazards, the data is not coherent with the classification.
  - » For class 1 of hazards, an expert judgment is required to interpret the data.

5.2 Case study No. 2– Di-isononyl phthalate (CAS 28553-12-0)

5.2.1 Resolution

Because it is a liquid substance, the following hazard classes are ruled out for di-isononyl phthalate:

- Flammable gases.
- Aerosols.
- Combustion gases.
- Pressure gases.
- Flammable solids.
- Pyrophoric solids.
- Combustion solids.

In addition, considering the chemical structure, the following hazard classes are ruled out (expert judgment):

- Explosives.
- Substances and mixtures which react spontaneously (autoreactive).
- Pyrophoric liquids.
- Substances and mixtures undergoing spontaneous heating.
- Substances and mixtures which, in contact with water, release flammable gases.
- Oxidizing liquids.
- Organic peroxides.
- Desensitized explosives.

For this case study, the purpose is to target the data search and give priority to it. This involves carrying out five searches:

1. EU Classification in the ECHA C&L database.
2. Japan classification in the NITE-J database.
3. New Zealand classification in the HSNO CCID database.
4. Searching relevant data in the ECHA-REACH database.
5. IARC assessment, in the IARC database.

1. Classification of the EU

Link to the ECHA C&L web page

The search result for di-isononyl phthalate - there is only one entry, with a registration status "REACH registration C&L". As seen in paragraph 4.4.1, the classification provided in the catalog reflects the classification proposed in the most notifications (not an official classification).

Classification:

- Not hazardous.

Link to the summary of notifications of ECHA C&L for di-isononyl phthalate

Classifications proposed:

- Acute toxicity (inhalation), category 4.
- Respiratory sensitization, category 1A
- Toxicity for reproduction, category 2.
- Hazards to the aquatic environment (chronic), category 1.

2. Classification of Japan

Link to the webpage of NITE-J for di-isononyl phthalate

Classification:

- Toxicity for reproduction, category 2.

3. Classification of New Zealand

Link to the web page of HSNO CCID for di-isononyl phthalate

Classification:

- Not available.

From the classifications found, and considering what was seen in paragraph 4.4.1, the following prioritization for the data search can be established:

a. Complete positive match.

None.

b. Partial match:

- Toxic for reproduction.
- Acute toxicity (inhalation).

- Respiratory sensitivity.
- Hazards to the aquatic environment (chronic).

c. Complete negative match.
   - Flammable liquids.
   - Acute toxicity (oral).
   - Acute toxicity (cutaneous).
   - Skin corrosion/irritation.
   - Serious eye injuries/ ocular irritation.
   - Cutaneous sensitivity.
   - Germ cell mutagenicity.
   - Carcinogenicity.
   - Specific target organ toxicity - Repeated exposure.
   - Aspiration hazard.
   - Hazards to the aquatic environment (acute).

4. Searching relevant data

There is a single entry: Active/Full (26/09/2022)

Link to the complete ECHA REACH Di-isononyl phthalate registration dossier

Only reliability data 1 and 2 are included.

- Toxicity for reproduction
  - » Toxicity for reproduction
    001 Key | Experimental result
    002 Supporting | Experimental result

  - » Developmental toxicity/teratogenicity
    001 Key | Experimental result
    002 Key | Experimental result
    003 Supporting | Experimental result
    004 Supporting | Experimental result
    005 Supporting | Experimental result
    006 Supporting | Experimental result
    007 Supporting | Experimental result

  - » Toxicity for reproduction: other studies
    002 Supporting | Experimental result
    006 Weight of evidence | Other result type

» Exposures related to observations in humans
003 Supporting | Experimental result
005 Supporting | Experimental result

- Acute toxicity
  - » Via inhalation
    001 Key | Experimental result
    002 Supporting | Experimental result
  - » Oral route
    001 Key | Experimental result
    002 Supporting | Experimental result
  - » Cutaneous route
    Link to the data
- Sensitivity
  - » Respiratory
    Link to the data
  - » Cutaneous
    001 Key | Experimental result
    002 Supporting | Experimental result
- Aquatic toxicity
  - » Long-term for fish
    001 Key | Experimental result
  - » Long-term for aquatic Invertebrates
    001 Key | Experimental result
    002 Supporting | Experimental result
    003 Supporting | Experimental result
  - » Algae and cyanobacteria
    002 Supporting | Experimental result
- Biodegradation

  001 Key | Experimental result
  002 Supporting | Read-across (Structural analogue/surrogate)
  003 Supporting | Read-across (Structural analogue/surrogate)
  004 Supporting | No specified result type
  005 Supporting | No specified result type

- Bioaccumulation
  - 001 Key | Experimental result
  - 004 Supporting | Read-across (Structural analogue/surrogate)
  - 005 Supporting | Read-across (Structural analogue/surrogate)
  - 006 Supporting | Experimental result
  - 007 Supporting | Other result type

- Partition coefficient
  - 001 Key | Experimental result
  - 002 Supporting | Experimental result
  - 003 Supporting | Experimental result

- Aquatic toxicity
  - » Short-term for fish
    - 001 Key | Experimental result
    - 002 Supporting | Experimental result
    - 003 Supporting | No specified result type
    - 004 Supporting | No specified result type
    - 005 Supporting | No specified result type
    - 006 Supporting | No specified result type
  - » Short-term for invertebrates
    - 001 Key | Experimental result
    - 002 Supporting | Experimental result
    - 003 Supporting | No specified result type
    - 004 Supporting | No specified result type
    - 005 Supporting | No specified result type

- Algae and cyanobacteria
  - 001 Key | Experimental result

- Flammable liquids
  - 001 Key | Experimental result
  - 002 Supporting | Experimental result

- Corrosion/irritation
  - » Skin corrosion/irritation
    - 001 Key | Experimental result
    - 002 Supporting | Experimental result
  - » Eye irritation
    - 001 Key | Experimental result
    - 002 Supporting | Experimental result

- Genetic toxicity
  - » In vitro
    001 Key | Experimental result
    002 Key | Experimental result
    003 Key | Experimental result
    004 Supporting | Experimental result
    005 Supporting | Experimental result

- Carcinogenicity
  001 Key | Experimental result
  002 Supporting | Experimental result
  003 Supporting | Experimental result
  004 Supporting | Experimental result

- Toxicity by repeated doses
  - » Oral route
    001 Key | Experimental result
    002 Supporting | Experimental result
    003 Supporting | Experimental result
    004 Supporting | Experimental result
    005 Supporting | Experimental result
    006 Supporting | Experimental result
    007 Supporting | Experimental result
    008 Supporting | Experimental result
    010 Supporting | Experimental result
    011 Supporting | Experimental result
    012 Supporting | Experimental result
    013 Supporting | Experimental result
    014 Supporting | Experimental result

  - » Via inhalation
    Link to the data

  - » Cutaneous route
    Link to the data

- Aspiration hazard
  001 Key | Experimental result
  002 Supporting | Experimental result
  003 Supporting | Experimental result

5. IARC Assessment

Link to access the IARC classification list

Result of the search: Not found in the classification.

5.2.2 Conclusions

From the analysis of the different classifications, 4 priority hazard classes were identified.

From the ECHA-REACH database 84 pieces of data categorized as reliable by ECHA were obtained and should be interpreted.

The interpretation of such data may require, to a greater or lesser extent, expert judgment.

5.3 Case study no. 3 - Ethylene oxide (CAS 75-21-8)

5.3.1 Resolution

As ethylene oxide is a gaseous substance, the following hazard classes are ruled out:

- Explosives.
- Flammable liquids.
- Flammable solids.
- Substances and mixtures which react spontaneously (autoreactive).
- Pyrophoric liquids.
- Pyrophoric solids.
- Substances and mixtures undergoing spontaneous heating.
- Substances and mixtures which, in contact with water, release flammable gases.
- Combustion liquids.
- Combustion solids.
- Organic peroxides.
- Desensitized explosives.
- Aspiration hazard.

In addition, considering the chemical structure, the following hazard classes are ruled out (expert judgment):

- Aerosols.
- Combustion gases.

In this case, the purpose is to obtain data to support our own classification, which involves two searches:

1. Searching relevant data in the ECHA-REACH database.
2. IARC assessment, in the IARC database.

Searching relevant data (ECHA-REACH)

There are six entries:

- Active/Full (10/26/2022).
- Active/Intermediate (10/31/2012).
- Active/Intermediate (10/31/2012).
- Active/Intermediate (10/31/2012).
- Cease Manufacture/Intermediate (10/31/2012).
- Cease Manufacture/Intermediate (10/31/2012).

Link to the complete ECHA - REACH ethylene oxide registration dossier

- Flammability

  001 Weight of evidence | Experimental result
  002 Weight of evidence | Experimental result
  003 Weight of evidence | Experimental result
  004 Weight of evidence | Experimental result

- Partition coefficient

  001 Key | Experimental result
  002 Supporting | Calculation
  003 Supporting | Calculation

- Acute toxicity
  - » Oral route

    001 Weight of evidence | Experimental result
    002 Weight of evidence | Experimental result
    003 Weight of evidence | Experimental result

  - » Via inhalation

    001 Key | Experimental result
    002 Key | Experimental result
    003 Supporting | Experimental result
    004 Supporting | Experimental result

  - » Cutaneous route

    Without reliable data.

- Corrosion/irritation
  - » Skin corrosion/irritation

    001 Key | Experimental result

  - » Eye irritation

    001 Supporting | Experimental result

- Sensitivity
  Without reliable data.

- Toxicity by repeated doses
  - » Oral route
    Without reliable data.

  - » Via inhalation

    001 Supporting | Experimental result
    002 Supporting | Experimental result
    003 Weight of evidence | Experimental result
    004 Weight of evidence | Experimental result

  - » Cutaneous route
    Without reliable data.

- Genetic toxicity
  - » In vitro

    001 Weight of evidence | Experimental result
    002 Weight of evidence | Experimental result
    003 Weight of evidence | Experimental result
    003 Weight of evidence | Experimental result

  - » In vivo

    001 Supporting | Experimental result
    002 Supporting | Experimental result
    003 Supporting | Experimental result
    004 Supporting | Experimental result
    005 Supporting | Experimental result
    006 Supporting | Experimental result
    007 Supporting | Experimental result
    008 Supporting | Experimental result

- Carcinogenicity
  S-01 Summary

- Toxicity for reproduction
  - » Toxicity for reproduction
    001 Weight of evidence | Experimental result
  - » Developmental toxicity/teratogenicity
    001 Weight of evidence | Experimental result
    002 Weight of evidence | Experimental result
- Exposures related to observations in humans
  - » Health vigilance data
    001 Supporting | Other result type
    002 Supporting | Other result type
    003 Supporting | Other result type
  - » Epidemiological data
    001 Supporting | Experimental result
    002 Supporting | Experimental result
    003 Supporting | Calculation
- Aquatic toxicity
  - » Short-term for fish
    001 Key | Experimental result
  - » Long-term for fish
    Without reliable data.
  - » Short-term for aquatic invertebrates
    001 Key | Experimental result
  - » Long-term for aquatic invertebrates
    Without reliable data.
  - » Toxicity for aquatic algae and cyanobacteria
    001 Key | Experimental result
    002 Key | Read-across (Structural analogue/surrogate)
- Biodegradation
  001 Key | Experimental result
  002 Supporting | Experimental result
  003 Supporting | Experimental result
  004 Supporting | Experimental result
- Bioaccumulation
  Without reliable data.

IARC Assessment

Classification: Group 1 (Link to access the IARC classification list).

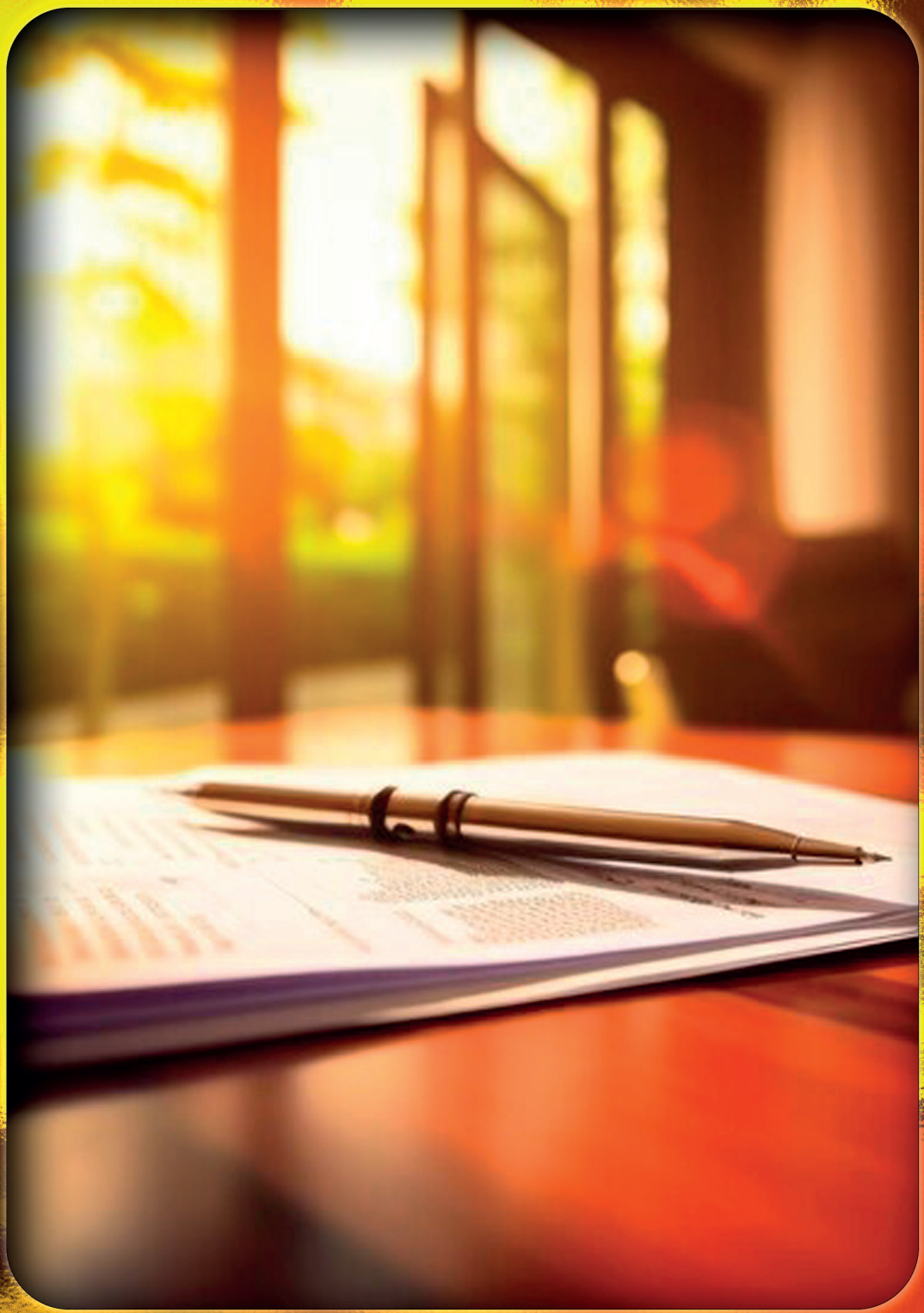
Monograph (Volume 100F, 2012):

- Limited evidence in humans.
- Sufficient evidence in animals.
- There is strong evidence that the carcinogenicity of ethylene oxide, a direct-acting alkylating agent operates by a genotoxic mechanism.

Expert judgment is required to classify in GHS category 1A or 1B.

5.3.2 Conclusions

- From the ECHA-REACH database, 50 pieces of data categorized as reliable by ECHA were obtained and should be interpreted.
- A classification and assessment has been obtained from the IARC database and the entire monograph (22 pages) should be read for a correct interpretation of the data.
- The interpretation of the data obtained may, to a greater or lesser extent, require expert judgment.



CONCLUSIONS AND RECOMMENDATIONS

Currently, the GHS is the chemical hazard classification and communication system implemented in many countries around the world, including Colombia.

Chemical manufacturers are primarily responsible for identifying and classifying their hazards and, based on the result of such classification, preparing the corresponding labels and SDSs.

Therefore, the correct classification of the hazards of chemical products is a critical aspect to achieve a safe and responsible use of these, at all stages of their life cycle.

In this context, it is essential to have properly trained professionals to correctly carry out the hazard classification process according to the GHS. This process consists of 3 steps:

1. Data collection.
2. Data analysis.
3. Decision on classification.

In these guidelines, the collection of data on substances from in-house tests and databases (step 1) was discussed in depth and elements were provided to complete or at least guide the data analysis (step 2).

The decision on classification (step 3) usually requires the judgment of experts with additional knowledge of chemical reactivity, toxicology, environment and the GHS itself.

Some additional sources of information on the GHS are:

- Virtual course " Clasificación y etiquetado de productos químicos según el SGA de la ONU [Classification and labeling of chemicals according to UN GHS]", eleven weeks long, in Spanish, delivered twice a year by UNITAR.
- Virtual course "Sistema Globalmente Armonizado de clasificación y etiquetado de productos químicos – SGA [Globally Harmonized System of Classification and Labeling of Chemicals – GHS]" in its basic, intermediate and advanced modules available through the Virtual Training School of Minambiente, designed and developed by the Ministry of Environment and Sustainable Development of Colombia.

- Guidance documents on GHS developed by the Ministry of Environment and Sustainable Development of Colombia, such as:
  - » Hazard communication guidance based on the criteria of the Globally Harmonized System of Classification and Labeling of Chemicals - GHS.
  - » National Strategy for the implementation of the Globally Harmonized System of Classification and Labeling of Chemicals - GHS - in Colombia (2016-2020).
  - » Intelligibility testing of the Globally Harmonized System of Classification and Labeling of Chemicals - GHS in Colombia.
  - » Hazard classification guidance based on the criteria of the Globally Harmonized System of Classification and Labeling of Chemicals GHS.

- Courses designed and developed by Responsabilidad Integral Colombia, including hazard communication under GHS, GHS basic, intermediate and advanced level GHS, implementation of GHS in workplaces based on the guidelines established in Resolution 0773 of 2021.

As presented, there is often no agreement among the experts themselves, which leads to the fact that today there is a globally harmonized system, but the classifications are not yet globally harmonized.

Finally, it is hoped that these guidelines will be useful to improve the processes of classification of chemicals according to the GHS, which should always be carried out with responsibility and full awareness of its importance to prevent damage to the health of workers and consumers, the environment and infrastructure.

Annex

Class of hazard	GHS (6th edition)	EU
Physical hazards		
Explosives	Unstable explosives 1.1 – 1.6	
Flammable gases	Cat. 1	
	Cat. 2	
Flammable aerosols	Cat. 1	
	Cat. 2	
Combustion gases	Cat. 1	
Pressure gases	Compressed/Liquified Refrigerated/ Dissolved	
Flammable liquids	Cat. 1	
	Cat. 2	
	Cat. 3	
	Cat. 4	
Flammable solids	Cat. 1	
	Cat. 2	
Auto-reactive substances	Type A – G	
Pyrophoric liquids	Cat. 1	
Pyrophoric solids	Cat. 1	
Products undergoing spontaneous heating	Cat. 1	
	Cat. 2	
Products which, in contact with water, release flammable gases.	Cat. 1	
	Cat. 2	
	Cat. 3	
Combustion liquids	Cat. 1	
	Cat. 2	
	Cat. 3	
Combustion solids	Cat. 1	
	Cat. 2	
	Cat. 3	
Organic peroxides	Type A – G	
Corrosive products for metals	Cat. 1	
Health hazards		
Acute toxicity	Cat. 1	
	Cat. 2	
	Cat. 3	
	Cat. 4	
	Cat. 5	

Class of hazard	GHS (6th edition)	EU
Cutaneous Corrosion/Irritation	Cat. 1	
	Cat. 2	
	Cat. 3	
Serious eye injuries/ ocular irritation	Cat. 1	
	Cat. 2A	
	Cat. 2B	
Respiratory or cutaneous sensitivity	Cat. 1A/1B	
Germ cell mutagenicity	Cat. 1A/1B	
	Cat. 2	
Carcinogenicity	Cat. 1A/1B	
	Cat. 2	
Toxicity for reproduction	Cat. 1A/1B	
	Cat. 2	
	Effects on or via lactation.	
Specific target organ toxicity - Single exposure	Cat. 1	
	Cat. 2	
	Cat. 3	
Specific target organ toxicity - Repeated exposure	Cat. 1	
	Cat. 2	
Aspiration hazard	Cat. 1	
	Cat. 2	
Environmental hazards		
Hazards to the aquatic environment (acute)	Cat. 1	
	Cat. 2	
	Cat. 3	
Hazards to the aquatic environment (chronic).	Cat. 1	
	Cat. 2	
	Cat. 3	
	Cat. 4	
Hazards for the ozone layer	Cat. 1	

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3. United Nations. *Recommendations relating to the transport of dangerous goods. Manual of tests and criteria, 7*th *revised edition, 2019.*

Globally Harmonized System of Classification and Labeling of Chemicals - GHS:

Data collection guidance on the classification of hazards

**"This is not the final version of this document.
The final version will be ready in September 2023;
nevertheless, the contents of the guidance will be the same".**

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ICCA International Council of Chemical Associations