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Expert Review for GHS Classification of Chemicals on Health Effects

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Abstract: Intoxication as a result of chemical accidents is a major issue in industrial health. The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) provides a framework for hazard communication on chemicals using labelling or safety data sheets. The GHS will be expected to reduce the number of chemical accidents by communicating the hazards posed and prompting safety measures to be taken. One of the issues which may be a barrier to effective implementation of the GHS results from discrepancies in GHS classifications of chemicals across countries/regions. The main reasons are the differences in information sources used and in the expertise of people making the classification (Classifiers). The GHS requests expert judgment in a weight of evidence (WOE) approach in the application of the criteria of classification. A WOE approach is an assessment method that considers all available information bearing on the determination of toxicity. The quality and consistency of the data, study design, mechanism or mode of action, dose-effect relationships and biological relevance should be taken into account. Therefore, expert review should be necessary to classify chemicals accurately. However, the GHS does not provide any information on the required level of expertise of the Classifiers, definition of who qualifies as an expert, evaluation methods of WOE or data quality, and the timing of expert judgment and the need for updating/re-classification as new information becomes available. In this paper, key methods and issues in expert reviews are discussed. Examples of expert reviews and recommendations for harmonized classification are also presented.

Key words: GHS, Expert review, Weight of evidence, Data quality, Classification, Health effects

Introduction

Intoxication caused by chemicals, including organic solvents, is one of the major issues in industrial health. More than 50 selected case examples per year are reported by the Japanese Ministry of Health, Labour and Welfare to illustrate the need for prevention of chemical accidents, and the occurrence factors including lack of recognition of hazards, insufficient education of safety and health, and non-use of personal protective equipment, etc[1)]. Implementation of the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) will make improvements to these situations. The GHS is a scheme recommended by the United Nations issued in 2003, which aims to enhance the protection of human health and the environment by providing an internationally comprehensible system for hazard communication[2)]. The classification and labeling of chemicals are key elements of industrial health to reduce the number of chemical accidents. Many efforts for implementation of the GHS are being made at national and international levels, since 2003. The efforts in Japan include issue of regulations (e.g., Revised Industrial Safety and Health Law), provisions of information for industries (e.g., Guidance on Consumer Product Risk Assessment for GHS Labeling, GHS Classification Guidance for Enterprises, or Support

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Tools for GHS Classification), education for GHS audiences (*e.g.*, holding of workshops or seminars, provision of education tools), or provision of GHS classification results of chemicals[3].

One of the issues on implementation of the GHS is discrepancies in GHS classifications of chemicals across countries/regions. As the GHS is a globally harmonized system, uniform GHS classification criteria are applied to each health hazard. However, different results of classification can be obtained for the same chemicals[4, 5]. The main reason is the difference in datasets (*i.e.*, information sources) used. The other reasons are adaptation of a building block approach[6] and the differences of expertise/experience of Classifiers[7]. The GHS is designed as a self-classification system, and it requires expert judgment in a weight of evidence (WOE) approach in the application of the criteria. The hazard classification process under the GHS is highly technical in nature, and it requires a certain background and level of expertise to perform it accurately. If a Classifier lacks understanding of the GHS classification criteria, the effort should be repeated by an expert or reviewed carefully before finalization of the results[7]. Therefore, an expert review process is important for GHS classification. However, the GHS does not provide any information on the necessary expertise of Classifiers, definition of the required expertise, evaluation methods for the WOE approach or data quality, and the timing of expert judgment. The authors have been involved in the review system for GHS classification projects for the Organization for Economic Co-operation and Development (OECD)[5] or in Japan[8]. Based on these experiences, key methods, examples, and recommendations on the application of expert review are presented in this paper.

Expert Review

Expert review for GHS classification in health effect is defined as evaluation process based on scientific evidence, expertise, experience, knowledge, and judgment in a WOE approach. Main targets of the evaluations are information sources, data quality, and WOE of the data. The experts should be people who have scientific knowledge, experimental skill and expertise in toxicology or industrial hygiene. They should understand well the classification criteria in the GHS and the regulatory sciences including test protocols. They should also recognize that the classification will be conducted based on hazard identification, not on risk assessment for humans.

Evaluation of information sources/datasets

One of the major factors of the different classifications for individual chemicals was the different sources used[4, 5]. Therefore, evaluation of information sources is an important factor for reliable classification. Experts know where to find the information necessary for classification and, more importantly, how to correctly interpret these data. Several types of information sources are available. These include review documents, peer-reviewed papers, industry based reports, abstracts, or databanks, etc. The most reliable source is international or national review documents in terms of the quality, availability and suitability of information that has to be used in decision making. Peer-reviewed papers and industry based reports have high quality and suitability, but low availability. Databanks have high availability, but low quality. Abstracts should not be used for classification without any supportive information. The age of the data differs among these sources. Newer information will be available from more recent documents, and this information could result in changed assessment of chemicals. Classification based on old or limited information will possess lower reliability. The evaluation of test results in each information source should be checked with multiple sources of information, if available. Original peer-reviewed papers are the best source for assessing difficult and comprehensive test results: these should be included in information collection, if possible.

Evaluation of data quality

Even for chemicals with testing data, inherent differences among test protocols and the interpretation of test data may confound hazard evaluation[9]. The determination of the quality of test data is a critical point for the classification. Therefore the evaluation of data quality has to be done by an expert. The evaluation of data quality includes assessment of three basic elements, *i.e.*, reliability, relevance and adequacy. Definitions of these terms are shown in Table 1[10].

In order to evaluate the reliability of the data, the following are examples of key points in an expert review[11]:

- Were the data obtained from the test using a standardized method (accordance with recent OECD test guideline or internationally recognized methods)?
- Was the test conducted in compliance with the principles of Good Laboratory Practice (GLP) or equivalent standards?
- Was purity or the physicochemical properties of the test chemical suitable for the test?
- Were the findings clear and plausible?
- Was the reporting information sufficient to make a judgment?

For regulatory purposes, a GLP study, in accordance

Table 1. Three basic elements of the evaluation of data quality

Element	Explanation
Reliability	Evaluating the inherent quality of a test report or publication relating to preferably standardised methodology and the way the experimental procedure and results are described to give evidence of the clarity and plausibility of the findings.
Relevance	Covering the extent to which data and tests are appropriate for a particular hazard identification or risk characterisation.
Adequacy	Defining the usefulness of data for hazard/risk assessment purposes. Where there is more than one study for each endpoint, the greatest weight is attached to the studies that are the most relevant and reliable.

Table 2. A scoring system to assess the reliability of toxicological data

Reliability of data	Explanation
Reliable without restrictions	Data generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline or in which all parameters described are closely related/comparable to a guideline method.
Reliable with restrictions	Data (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable.
Not reliable	Data in which there were interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g. unphysiological pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment.
Not assignable	Data which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.).

with standardized methods, has a high level of reliability in toxicology. On the other hand, a research oriented study may be of low reliability. A scoring system to assess the reliability of toxicological data is shown in Table 2[10, 11].

Examples of key points of evaluation of the relevance of the data are as follows[11]:

- Was the study design suitable? It should include vehicle, animal species, route of administration, doses or concentration used, parameters examined, etc.
- Were there dose-effect relationships?
- Was the effect of statistical and biological significant?
- What test system was used (*e.g.*, *in vitro*, *in vivo*, or human)?

The level of relevance of toxicological findings will be higher usually in the following order: i) human data (meta-analysis, randomized controlled trial, case control study, cross-sectional study, and case report); ii) animal data (primate, rodent, other mammals, non-mammals); iii) *in vitro* data (mammalian cells, microorganisms, biochemical reactions).

Examples of key points of the evaluation of the data adequacy are as follows[11]:

- Recognition of the strengths and weaknesses of the test method (*e.g.*, sensitivity, specificity, accuracy).
- What was the key study?
- Was the finding supported by other data?
- What kind of mechanisms or mode of action was involved?

The above key points are important for *in vitro* data, *in silico* data, or human data. The level of adequacy of any toxicological findings will be higher usually in the following order: i) similar findings in more than single study; ii) the findings obtained with a validated test method; iii) the finding is supported by the other data; iv) single study; v) *in silico* data.

Evaluation of WOE among the data

Generally, three objectives of the WOE approach are suggested for regulatory decision-making: i) provision of a "clear and transparent framework" for evaluation of the evidence in risk determination; ii) offer of a consistent and standardized approach to evaluating toxic substances submitted to regulatory agencies; and iii) help of identification of the discretionary assumptions in risk determinations from experts[12–14]. The GHS defines WOE as follows[2]: "All available information bearing on the determination of toxicity is considered together, including the results of valid *in vitro* tests, relevant animal data, and human experience such as epidemiological and clinical studies and well-documented case reports and observations. Both positive and negative test results are assembled together in the weight of evidence determination. However, a single positive study performed according to good scientific principles and with statistically and biologically significant positive

results may justify classification." When multiple data for one endpoint exist, the WOE approach must be applied by experts. Toxicology experts must consider all available data (both positive and negative), weigh it with respect to validity, and finally reach a conclusion. In a WOE approach, quality and consistency of the data, study design, mechanism or mode of action, dose-effect relationships, reproducibility, biological relevance, strength of the evidence, and purity of the test substance should be taken into account. It is noticed that any discrepancy in classification will be based on the different weighting evidence used from expert to expert. Harmonization of expert judgment is not easy, and is not static[7].

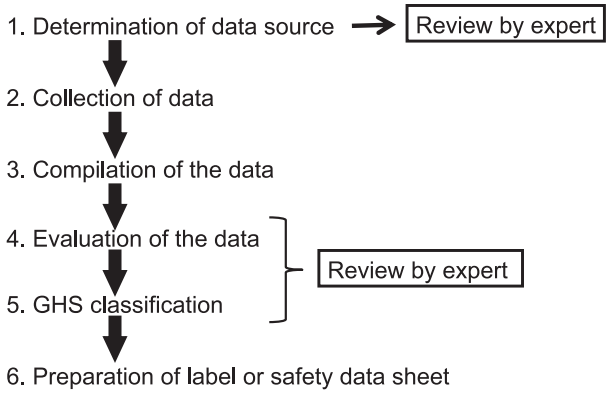

Fig. 1. Timing of expert review.

Issues in Expert Review

Expert review should promote and reflect the objective consideration of the full weight of evidence from alternative information sources, taking into account quality of data (*i.e.*, reliability, relevance and adequacy)[9]. The issues in expert review include: i) a single opinion from an expert might be low on transparency and high on subjectivity; ii) consistency of the judgment is unclear on between experts.

Transparency and objectivity

A WOE approach is one of key elements of expert review. Therefore, issues in applying it are also ones that might confound an expert review. The term WOE does neither constitute a scientifically well-defined term nor an agreed formalized concept characterized by defined tools and procedures. It is not clear which methods may be used, how they may be applied to the scientific evidence, what the results might be and how these may be used to make decisions in a specific hazard identification[14, 15]. The issues of a WOE approach in GHS classification include: i) application of WOE depends on the expertise of experts; ii) there are no canonical frameworks for weighting scientific evidence; iii) a process methodology is low on transparency and high on subjectivity; iv) WOE is usually applied in the case where there is no conclusive single study in demonstrating a cause-effect relationship; v) WOE looks like a 'seat-of-the pants' qualitative assessment. Without an explanation of how evidence is "weighed" or "weighted", the WOE approach may be to be a "black box" of scientific judgment[13]. To keep transparency of expert reviews, the review should be objective and taken into consideration of evidence based toxicology[16].

Consistency

Consistency of the results of expert review on similar subjects is a fundamental principal for hazard classification of chemicals. The outcome from an expert should be consistent in between experts and in chronological order if no new data or scientific evidence is available.

Timing of expert review

The practical application of an expert review (*i.e.*, how and when that review should be applied) is not mentioned in the GHS. This can result in ineffective hazard classification, hazard communication and chemical management[9]. Based on the experiences from the GHS classification projects, suitable timing of expert review is proposed (Fig. 1). General steps of GHS classification are as follows: Data collectors gather available data with a certain list. Classifiers read, select, compile and evaluate the information (*i.e.*, data), and then classify the chemical based on GHS criteria. Information gathering is the first step of hazard classification of chemicals. Different information source sets result in different classification results. It is important for GHS classification to establish useful and effective information source set. Experts should review suitability of the information sources at the beginning of GHS classification work, and should provide sufficient list of data sources. Examples of the sources are provided by Japan Ministry of Economy, Trade and Industry (METI)[17] or European Chemicals Agency[18]. Experts will review the necessity of additional source(s). Next timing of expert review is at time of evaluation of the data and following assignment of classification by Classifiers. Experts should review the relevance of the classification assigned by classifiers based on data quality of key studies and total weight of evidence of the findings[7].

Examples of Expert Reviews Where Re-classification Was Needed

Followings are examples of expert review in Japanese

GHS classification projects. Details of some examples are available from the web site of METI[19]. Examples for germ cell mutagenicity are given in a previous article[7].

Antimony trioxide [1309-64-4]

The original classification for this compound was Category 2B in regard to eye irritation, based on a mild irritation seen in rabbits[20]. An expert pointed out that draft EU Risk Assessment Report evaluates this compound as non-irritant based on the result from a new GLP study. The draft is not available yet, but the original test report is available through the OECD[21]. As the result is now non-irritating in the rabbit, "Not classified" was re-assigned in the review. This case suggests the importance of data collection.

4,4'-Thiobis(6-tert-butyl-m-cresol) (TBBC) [96-69-5]

The original classification was Category 1 in skin sensitization based on two patients with positive patch tests to TBBC who developed contact dermatitis to TBBC-containing latex gloves[22]. An expert questioned the reliability and relevancy of this information. The American Conference of Governmental Industrial Hygienists summarized that sufficient data were not available to recommend sensitization notation[22]. Therefore, "Classification not possible" was assigned by expert review. The point of debate was the evaluation of data quality.

p-Dichlorobenzene [106-46-7]

The original classification was Category 2 for germ cell mutagenicity based on a negative result from a dominant lethal test and a positive result in a micronucleus test[23]. However, a reviewing expert noticed that both positive and negative results existed for micronucleus tests of this compound. The positive result was not confirmed by additional tests including tests using a similar protocol to the first test. A positive result in a kidney micronucleus test was considered of low reliability and relevancy. Another 5 or more micronucleus tests showed negative results. Based on WOE, "Not classified" was assigned by the expert. The reasons for the changed classification were that multiple negative results had more weight than a single positive result and also an evaluation of data quality for the original positive result.

Styrene [100-42-5]

The original classification was Category 2 for carcinogenicity based on the classification in Group 2B by evaluation of International Agency for Research on Cancer[24]. A reviewing expert suggested that a recent analysis revealed that lymphatic and haematopoietic neoplasms seen in humans exposed to styrene are likely to be due to concomitant exposure to butadiene[25]. Mouse specific mode of action (MOA) exists in the induction of mouse lung tumor[26]. Opinions on the interpretation of the cancer data were different among experts. Finally, after much discussion resulted in a "Not classified" Category instead of Category 2. Thus the change in Classification resulted from the recent re-evaluation and analysis of the MOA.

Ethylene glycol [107-21-1]

The original classification was Category 1B for reproductive toxicity based on reduced skeletal ossification and malformations of the skeleton, which were observed without maternal toxicity[27]. A reviewing expert pointed out that the above effects were seen in rats at 1,500 mg/kg (over the limit dose of 1,000 mg/kg) or mice at 500 mg/kg. The expert introduced a recent evaluation document[28] which mentions that ethylene glycol is not directly responsible for developmental toxicity, but that this toxicity is due to the accumulation of glycolic acid (a metabolic breakdown of ethylene glycol). The saturation level of this compound is lower in humans than that in rodents. There is negligible concern (at current human exposure levels) for reproductive toxicity in humans. Therefore, "Not classified" was assigned by an expert review. The relevant points for the change in classification were the effective dose for toxicity shown in animal experiments which was not relevant to human exposure and the findings of different metabolism in human compared to rats for this compound.

Hydroquinone [123-31-9]

The original classification was Category 1B for reproductive toxicity based on an increase in foetal resorptions[29]. A reviewing expert pointed out that the above finding was based on old (1955–1964) studies. Recent evaluations generated negative results in rat and rabbit developmental tests and a rat two generation fertility test[30, 31]. These tests were conducted in accordance with recent guidelines, giving more reliability. Therefore, "Not classified" was assigned by the expert review for reproductive toxicity.

With respect to specific target organ toxicity (single exposure), the original classification was Category 1 (central nerve system and kidney) based on the appearance of tremor, vomiting and cyanosis which was observed in exposed humans and the observation of kidney damage in rats[29]. However, a reviewing expert pointed out that the human findings were based on exposure to mixtures containing hydroquinone plus other substances. Symptoms observed after exposure to

hydroquinone alone were transient central nerve system effects.

The rat is unique in susceptibility to kidney effects following hydroquinone exposure[31]. Based on the new evaluation document, Category 3 (narcotic effect) was assigned by an expert review. The relevant points for the change in classification were insufficient information gathering in the first instance, careful review of the documents and use of recent evaluation using more reliable data.

Ferric Chloride [7705-08-0]

The original classification was Category 1 for aspiration hazards based on the following finding[32]; a woman presented with vomiting after ingestion of 200 ml ferric chloride solution (pH 1.0). Three hours after her ingestion she presented with drowsy consciousness, tachycardia and protracted vomiting. Aspiration pneumonia was also noted. A reviewing expert noticed that the aspiration pneumonia was observed after vomiting of a corrosive solution, which does not necessarily indicate an aspiration hazard. In addition, the findings did not fit the GHS criteria for aspiration hazard. Therefore, "Classification not possible" was assigned by the expert review. The relevant points were recognitions of the definition in the GHS text and the effect by ingestion of a corrosive solution.

Recommendations

Consideration of different information sources can result in different GHS classification results. Judgments of data quality and weight given to findings will vary among experts. To minimize these variations, the following approaches will be needed for harmonized classification: i) Development of an internationally-constructed and maintained information database for GHS classification; ii) Provision of rationales of selection of (key) studies and a classification derived from them for maintaining transparency; iii) Discussion on how to apply expert judgment and how to assess the quality of data from limited studies; iv) Establishment of a GHS classification data bank which collects GHS classification results including related information; v) International review system of classification on specific chemicals; and vi) Consultation system for companies/Institutes without experts. These will be help the harmonization and transparency of GHS classifications. Duplication of classification will be also avoided.

Conclusions

It is clear that suitable classification depends on the correct interpretation of the data, the application of the weight of evidence approach and basing judgments only on high quality data. Toxicologists or industrial hygienists, as experts, play an important role in assigning supportable classifications. They should consider data quality, and should review critically several authoritative documents including original articles to support the classification of chemicals.

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