THE FORTHCOMING SEVESO III DIRECTIVE: ALIGNMENT WITH GHS CLASSIFICATIONS AND DATA ISSUES FOR ACUTE TOXICITY†

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The Seveso III Directive is currently in negotiation and a revised version of the COMAH Regulations 1999 is due to come into force in 2015. A key change will be the use of the Globally Harmonised System (GHS) of classification to set qualifying quantities to determine the scope of the Directive. For the classification of acute toxicity, the alignment of GHS with Seveso is not straightforward because the GHS classification differs from that used in the current Dangerous Substances Directive 1996 (DSD).

The paper gives the background to Seveso III and discusses alignment issues for the classification of acute toxicity. A survey of UK COMAH sites has been carried out to help understand the possible impact of the directive on UK industry. The results of this survey are discussed, focusing the issue of the availability of data for determining the GHS classification for acute toxicity. Substantial problems were found with using MSDS data to obtain the GHS classification. Methods for determining the GHS classifications are presented for pure substances and for mixtures.

KEYWORDS: Seveso III, GHS, classification, CLP, acute, health, toxicity, MSDS

1. INTRODUCTION

The Seveso III Directive is currently in negotiation and a revised version of the COMAH Regulations is due to come into force in 2015. The proposal for Seveso III (EC, 2010) was published in December 2010. The main reason for the new directive is the replacement of the Dangerous Substances Directive (DSD) (EC, 1967) and Dangerous Preparations Directive (DPD) (EC, 1999) with Classification Labelling and Packaging Regulations (CLP) (EC, 2008) which use the Globally Harmonised System (GHS) of classification of chemicals. The scope of the Seveso II Directive (EC, 1996) as amended, which is implemented in the UK as the COMAH Regulations, was linked to classifications in the DSD which determine the qualifying quantities for sites to be top tier or lower tier. The scope of the Seveso III Directive will instead be linked to GHS classifications. Additionally, the main changes in the EC proposal include provision of public information and public consultation, prescriptive minimum inspection frequencies (once per year for top tier sites and every 3 years for lower tier), enhanced provision for derogation from the requirements of the Directive, and consideration of the need to protect the environment in land-use planning.

This paper is concerned with potential changes to the scope of the COMAH regime in the UK as a result of classification changes for acute health effects. This is the major effect of the classification changes and is dependant on how the Seveso III Directive threshold quantities align with the new classification categories. This is discussed further below.

The objectives of the work described here were to support the UK in negotiations of the text of the Seveso III Directive by better understanding the potential impacts on UK industry and regulators. Earlier work on the potential impacts for the UK had been carried out by Trainor et al (2008a,b) but this did not address the alignment in the Seveso III proposal.

2. SEVESO III ALIGNMENT WITH GHS

2.1 COMPARISON OF CLASSIFICATION SYSTEMS

The DSD/DPD define two categories for acute toxicity which align with Seveso II threshold quantities. These are 'toxic' (T) and 'very toxic' (T+). In addition, there is a 'harmful' (Xn) category which is out of scope of Seveso II. CLP uses the GHS acute toxicity categories 1, 2, 3 and 4. For both systems, categories can be defined according to the lethality response for the oral, dermal or inhalation exposure routes. Criteria are in terms of the LD_{50} (dose which will kill 50% of a test population) or the 4h LC_{50} (concentration which will kill 50% of a population given a 4 hour exposure). The physical form of the substance (vapour, liquid or solid aerosol, or gas) is also taken into account for the inhalation route.

Figure 1 shows the relationship between these old and new categories. The dark blue vertical line represents where the T+/T boundary was for the old system. The lighter blue vertical line shows the same thing for the T/Xn boundary. These lines go through the middle of many of the GHS categories, so some substances that are category 3 for oral,

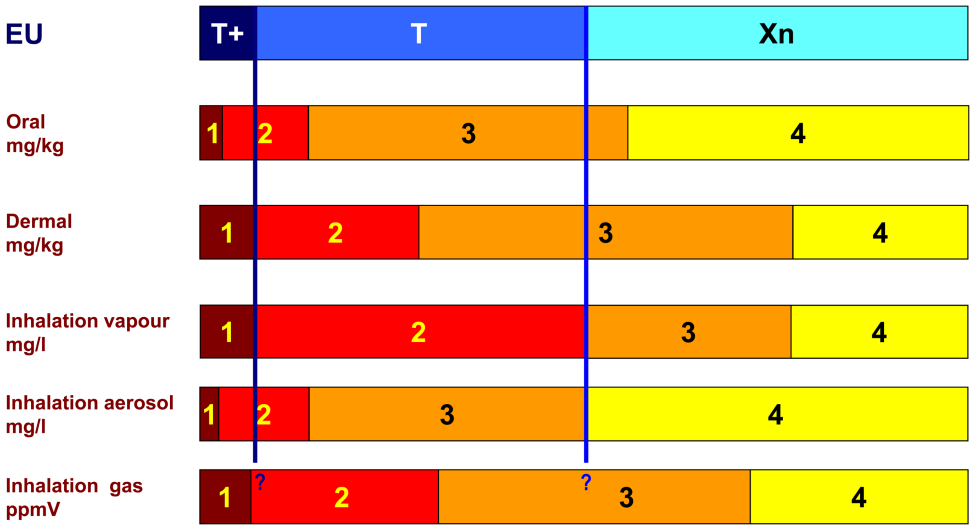

Figure 1. Comparison of criteria between the EU (DSD/DPD) and GHS acute toxicity categories

would previously have been labelled as toxic, whereas others, with a lower LD_{50} but still category 3, would have previously been classed as harmful. Category 3 for dermal has the same problem. It can also be seen that category 2 for oral intake and for inhalation of aerosols consists of substances that are currently labelled as T+ or T.

For inhalation of gases and "vapours near the gaseous state", GHS uses different units (parts per million by volume or ppmV) whereas the units used under Seveso II are mg/litre (mg/L). The use of ppm instead of mg/L can have a dramatic effect on how a substance is classified, particularly for those substances with a low molecular weight. This was discussed by Trainor et al. (2008a). As a result, some additional substances (ammonia, boron trifluoride and hydrogen sulphide) have been made into new named substances in the Seveso III proposal. As a result, the two classification systems cannot be compared directly for the inhalation of gases; the position of the blue lines for the gases will be different for every single substance because concentration in ppmV is dependant upon the molecular weight.

2.2 PROPOSED SEVESO III ALIGNMENT (E* ALIGNMENT)

The alignment proposed for Seveso III (EC, 2010) has been termed the E* alignment (COWI, 2010). It is shown in Figure 2. The shaded areas show how the GHS categories would be treated under Seveso III. The dark blue shaded areas cover category 1 and these would be given the same qualifying quantities as those for 'very toxic' (T+) in

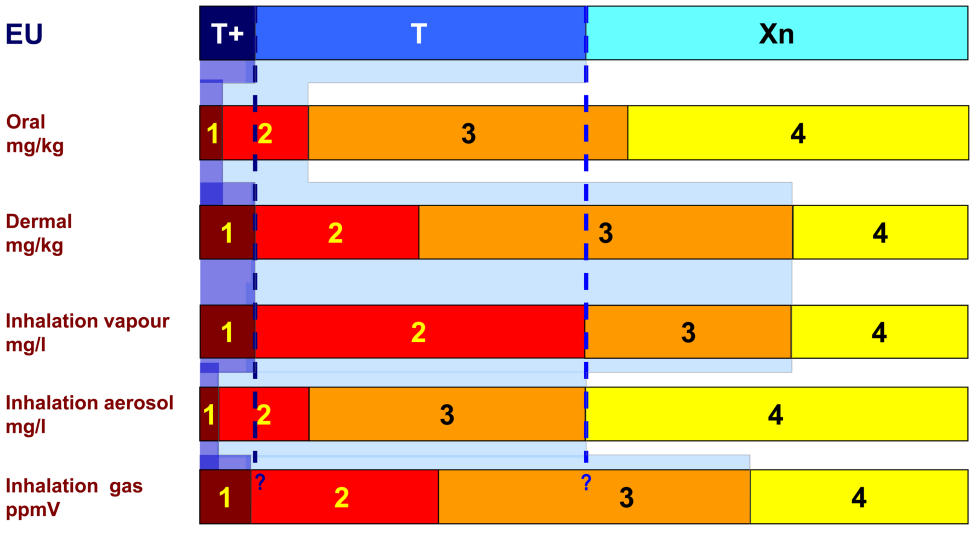

Figure 2. The proposed alignment (E*) between Seveso III and GHS

Seveso II. The lighter blue shading shows those GHS categories which would be given the same qualifying quantities as 'toxic' (T) under Seveso II.

All the potential alignments involve compromises because the two classification systems are different. Key changes under this alignment option are:

- Some substances which are currently classified as very toxic (T+) (oral and inhalation aerosol exposure routes) will become GHS category 2 and given larger qualifying quantities, equivalent to substances with a current classification of toxic (T). Their contribution to whether a site was top-tier, lower tier or out of scope of Seveso would therefore be reduced due to the change in classification.
- Many substances which are GHS category 3 by the oral route are currently classified as T, but under the proposed alignment they would fall out of scope.
- Some substances which are GHS category 3 by the dermal or inhalation vapour route are currently classified as harmful (Xn). These would come into scope. There may also be similar substances which are GHS category 3 by the inhalation gas route, but the comparison is more complicated because of the different units (see 2.1 above).

2.3 ALTERNATIVE ALIGNMENT OPTIONS

A number of other alignment options have been discussed as part of the negotiations. These include the 'Simple' alignment (Figure 3), which was discussed by Trainor et al (2008a,b), and the 'E' alignment shown in Figure 4 (COWI, 2010).

Key changes under the 'Simple' alignment (Figure 3) would be that:

- As with the E* alignment, some substances which are currently classified as T+ (oral and inhalation aerosol exposure routes) will become GHS category 2 and given larger qualifying quantities equivalent to T.
- Many substances which are GHS category 3 by the oral, dermal, inhalation aerosol and inhalation gas routes, are currently classified as T, but under the proposed alignment they would fall out of scope.

Although there is potential reduction in the scope of Seveso based on the 'simple' alignment, a qualitative study by Trainor et al (2008a) suggested that few if any UK sites would reduce their COMAH status.

The E alignment (Figure 4) is similar to the E* alignment except that substances which are category 3 by the dermal route would not newly come into scope.

3. UK SURVEY OF COMAH SITES

The EC carried out a study (COWI, 2010) to inform their impact assessment of Seveso III alignment options, but this considered the impacts in terms of the number of substances that could change scope, which does not necessarily equate to the number of sites changing scope. However, in order to determine the impact in terms of numbers of sites which would change their Seveso status, considerable data are needed in terms of the substances and quantities held by each site. Moreover, there is a need to identify substances which could newly come into scope. Trainor et al. (2008) had attempted to do this by considering high tonnage substances in the IUCLID database (OECD, 2012) but it was considered unlikely that all such substances were successfully identified, and there were also issues with the quality of the data available.

In order to obtain such information, HSE commissioned ORC International to carry out a survey of UK COMAH sites (ORC, 2011). Two questions in the survey related to assessing the impact of different alignment options for acute toxicity. Question 7 asked for on-site tonnages of

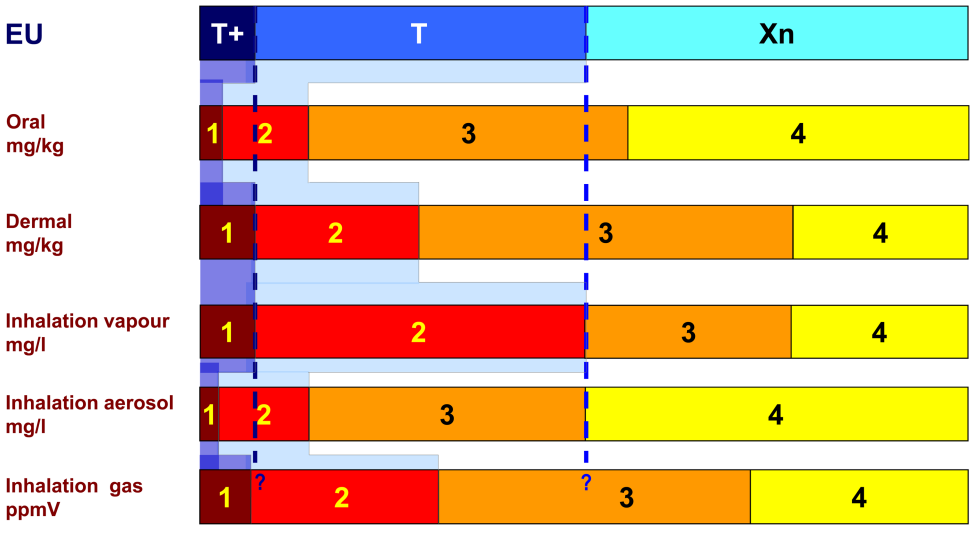

Figure 3. 'Simple' alignment between Seveso III and GHS

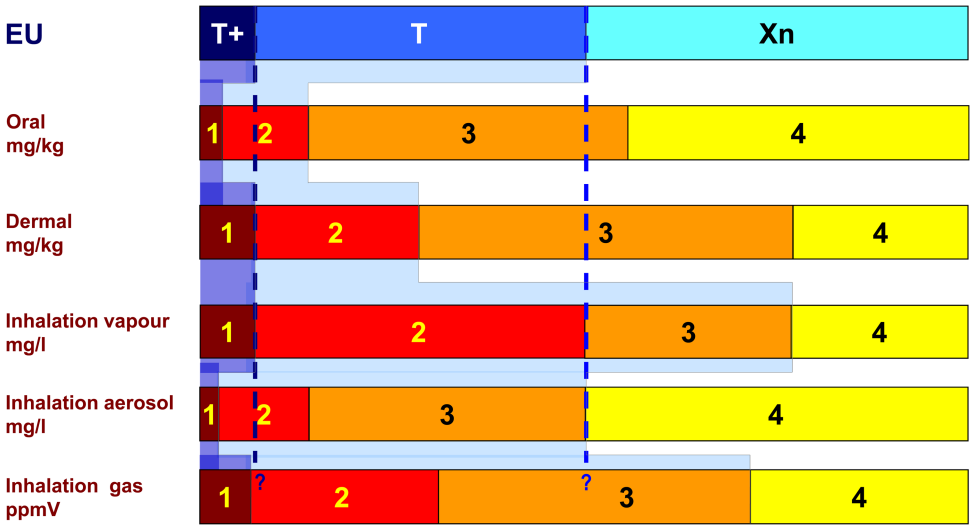

Figure 4. E alignment between Seveso III and GHS

substances which Trainor et al. (2008a) had already identified as being relevant. Question 8 asked for information and on-site tonnages of any other substances or mixtures which were classified as T+, T or Xn. In addition, to obtain the necessary toxicity data to allow the identified substances to be classified under GHS, material safety datasheets (MSDS, referred to as Safety Data Sheets in the REACH legislation (EC, 2006)) were requested for each substance identified. At that time, no information on harmonised classifications under CLP nor notifications under REACH was available. Use of data from MSDS was a compromise to reduce the burden on industry in supplying toxicity data and to be able to obtain results early enough to usefully inform the negotiations. It was anticipated that the MSDS data would not be ideal but it was found to be worse than expected. We carried out a partial analysis of the impact of different alignment options for the UK and this was reported by ORC (2011). A more detailed analysis will be the subject of a separate paper. The current paper is concerned with the data quality issues, which could prevent companies from determining how Seveso III will affect them, and methods for obtaining the necessary data to allow classification.

4. DATA ISSUES

4.1 ISSUES WITH MSDS

1642 substances and mixtures were identified and analysed. Figure 5 presents the overview of the statistics:

- Only 17% of the MSDS contained the toxicity data necessary to determine the GHS classification;
- 54% of the MSDS contained limited toxicity data;
- 29% of the MSDS contained no toxicity data at all.

To allow classification, data are needed about the LD/LC_{50}. However, LD_{50} and LC_{50} are not definitive values, and they can vary significantly depending on several factors:

- The test conditions used to perform the acute toxicity experiments;
- The animal species and strain used;
- The duration of the test;
- The physical state of the substance when tested (required for inhalation LC_{50});
- Numbers of animals used in the test.

Therefore, in order to use a LD_{50} or LC_{50} value for classification, this should have been determined in a well-reported study, conducted according to scientifically valid methods (for example the OECD Guidelines for the Testing of Chemicals), and preferably in compliance with the principles of Good Laboratory Practice (GLP). For the inhalation route, it is vital that information on the duration of exposure and physical state of the tested substance is available. Where several acute toxicity studies with differing results

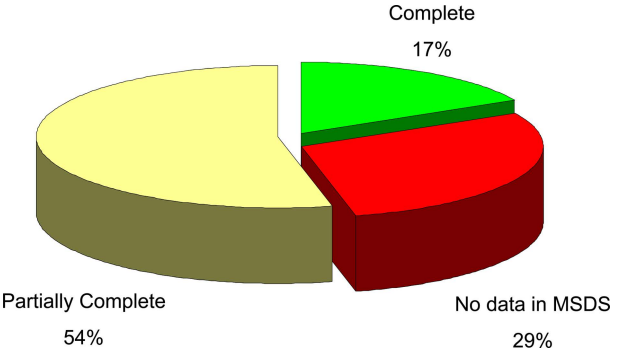

Figure 5. Quality of MSDS data provided by respondents to the survey of UK COMAH sites

are available for an exposure route, a weight of evidence approach, using expert judgement, must be used to determine the classification.

From our experience, we have found that the majority of MSDS do not specify the details required to make an informed classification. Issues with MSDS for pure substances are summarised in Table 1. Not only did this make analysis of the survey results difficult, it means that companies may find it difficult to work out the effect that the change to the Seveso III Directive will have on them, in cases where the GHS classification of substances are not available. However, obtaining data from MSDS is not the only option, as described below. Furthermore it is anticipated that over time, the relatively new REACH regulation (EC, 2006) will improve access to the available toxicity data.

When dealing with mixtures, unless the mixture itself has been tested to derive LD_{50}/LC_{50} data (or there is a similar substance that data can be derived from), all of the details needed to align substances are required for each of the major ingredients. This includes the concentration of ingredient in the mixture, LD_{50}/LC_{50} values, the concentration tested, the duration of exposure and physical state tested for the inhalation route, the animal species used, the test conditions used and the source of the data. Therefore, all of the issues associated with assessing pure substances are relevant for each of the ingredients, so depending on the number of ingredients, the number of problems encountered could be multiplied several fold. A number of additional problems encountered when reviewing MSDS for mixtures are shown in Table 2.

4.2 EFFECTS OF DIFFERENT STUDIES

As described above, MSDS were used, so far as was possible, to determine the GHS category for identified substances. It was not possible to do this for most of the mixtures due to the issues noted in Table 2.

Even when complete data were available from an MSDS, this was not necessarily for the most appropriate study. One of the outputs from this work was a list of substances which were in GHS category 3 but which are currently classified as Xn. Such substances would therefore have potential to bring new sites or even new sectors into scope. A more detailed peer review of the acute toxicity of these substances was carried out by a HSE expert toxicologist who assessed data obtained by searching the additional information sources discussed in section 5 below. Of the 47 such substances identified, only 18 (38%) were confirmed as being in category 3.

Table 1. Data issues with MSDS for pure substances

1	The source of the acute toxicity data is not stated so its reliability is unclear.
2	Many MSDS do not state the animal species used in the test or, in the case of the inhalation route, the duration of exposure.
3	In relation to the inhalation route, most MSDS do not declare the physical state the substance as tested, and therefore the GHS classification category cannot be determined.
4	Some LD_{50} values reported are for a similar substance, not the substance itself. (Expert judgement must be used to decide if it is appropriate to read-across acute toxicity data between substances.)
5	Most MSDS do not provide the molecular weight of the substance.
6	Some of the LD_{50} values are cited without the units being specified.
7	Some MSDS do not state whether the value quoted is an LD_{50} or LC_{50}.
8	MSDS vary between different countries in both quality and the information provided. This is dependant on the particular countries' regulatory requirements. Many of them will not provide an LD_{50} at all.
9	Many MSDS do not provide any LD_{50} or LC_{50} values, or do not include LD_{50} or LC_{50} values that are available.
10	Those MSDS that do provide LD_{50} or LC_{50} data, rarely have them for all 3 exposure routes, possibly because acute toxicity studies have not been conducted for all exposure routes.

Table 2. Data issues with MSDS for mixtures

1	Some MSDS do not specify the components of a mixture or their concentrations. MSDS for solutions do not always provide details of the diluent.
2	Many MSDS do not provide definite concentrations, but will give a range of concentrations instead. In this study, we used a worst-case approach, but this could drastically affect the resulting category.
3	It can be unclear whether the MSDS refers to a pure substance or a mixture, especially if the product has a trade name.
4	Sometimes LD_{50} or LC_{50} values are cited but it is not clear if they refer to individual components of the mixture or to the mixture itself or even to a similar mixture.
5	In many cases the MSDS has the LD_{50} for one or some, but not all, of the ingredients. In these cases the MSDS alone cannot be used to estimate the LD_{50} for the whole mixture.
6	When LD_{50} values are provided, MSDS do not always state the concentration of the substance that was used to measure them.
7	A substance or mixture may have been modified on site, for example it could have been mixed with another substance or diluted. In such cases, the MSDS used by the company will generally only apply to the material that was originally purchased and not to the material that is stored on site.

5. METHODS FOR DETERMINING GHS CLASSIFICATIONS

5.1 PURE SUBSTANCES

It is possible that the GHS classification for a substance is already available. The ESIS and ECHA websites (see below, also summarised in Table 3) contain such data where available. If not available, the GHS classification will need to be derived from LD_{50} or LC_{50} data.

It is extremely important that the LD_{50} or LC_{50} data are derived from reliable studies, as discussed in Section 4.1. LD_{50} or LC_{50} values presented in peer-reviewed reports emanating from EU regulatory processes, for example in conclusions to Existing Substances Regulation Risk Assessment Reports, from EU pesticide review reports, or from OECD, IPCS and US EPA reports can be assumed to be reliable.

Table 3 shows some useful on-line databases and search tools which could be used to obtain LD_{50} or LC_{50} data:

- ESIS: This is the European Chemical Substances Information System. It is a search tool from the European Commission and the data have been evaluated by the EU. The CLP/GHS tool (within ESIS) gives the official list of harmonised classifications according to the CLP Regulation (EC, 2008); these are legally binding within the EU. It should be noted that the GHS acute toxicity categories presented in the CLP Regulation are minimum classifications that should only be applied if data (such as LD/LC_{50}) are not available to show that a more severe category should be applied. It also provides downloadable files such as Risk Assessment Reports and IUCLID datasheets. The Final Risk Assessment Report will have been peer reviewed and agreed by the EU.
- INCHEM: This is a search tool produced by the International Programme on Chemical Safety and the Canadian Centre for Occupational Health & Safety.
- ATSDR: The Agency for Toxic Substances and Disease Registry are a federal public agency in the US. The quality of these data is good.
- eChem Portal: This is a search tool run by the OECD in collaboration with several bodies: WHO, IPCS, UNEP, ECHA, EC, ICCA and BIAC. It links to other data sources, various OECD schemes, IUCLID and other search tools. eChem Portal provides descriptions of the sources, links to the individual databases, links to any disclaimers and the peer review that the data have undergone for each participating scheme.
- IRIS (Integrated Risk Management System): This is available through the US EPA (Environmental Protection Agency). It has both a searchable tool and an A to Z list of substances. The quality of the data is good.
- ECHA (European Chemicals Agency): This website includes a recently developed Classification and Labelling database and dossiers for substances registered through REACH. ECHA has a disclaimer on the site to say that they have not checked the data; it is not peer reviewed; it is subject to change and that users should proceed with caution. Harmonised data from Annex VI of the CLP regulations are also included and can be found by searching with the "harmonised data only" box checked. Other data on this website, such as information extracted from REACH registration dossiers, have not been peer reviewed, although it will often be possible make a judgement on the reliability of these data.

Although these resources provide information about the amount of peer review that the data have undergone, many of them also include data which have not yet been reviewed. Therefore it is important to check the quality of the data when using an LD_{50} or LC_{50} value. The data should be in the appropriate units and for the preferred animal species (according to the test guidelines) to be used for GHS classification. Requirements are given in Table 4.

In addition, inhalation lethality data must relate to an exposure duration of 4 hours to determine the classification. The CLP regulations state that for data obtained for a 1 hour exposure, the LC_{50} should be divided by 4 for aerosols and by 2 for vapours and gases to extrapolate to a 4 hour exposure period. However, they do not state what to do for other time periods. In such cases, the extrapolation method proposed by National Research Council (2001), based on ten Berge (1986), may be appropriate.

Table 3. Toxicity databases and search tools

Resource	What does it contain?	Website
ESIS (from EC)	Several tools, e.g. EINECS, ELINCS, BPD, CLP/GHS tool	http://esis/jrc.ec.europa.eu
IPCS INCHEM	Search tool of peer reviewed data e.g. CICADS, PIMS, EHC, UKPID	http://www.inchem.org
ATSDR website	Substance index in alphabetical order	http://www.atsdr.cdc.gov
eChem Portal (run by OECD)	Links to data sources, e.g. OECD schemes, IUCLID & search tools	http://www.echemportal.org
IRIS (from US EPA)	A to Z list of substances & search tool	http://www.epa.gov/iris
ECHA website	C&L database, dossiers for registered substances	http://echa.europa.eu

Table 4. Data requirements for GHS classification

Exposure route	Measurement	Preferred test species	Physical state	Units	Source of data
Oral	LD_{50}	Rat	N/A	mg/kg body weight	From a reliable, peer-reviewed source
Dermal	LD_{50}	Rat or rabbit	N/A	mg/kg BW	
Inhalation	LC_{50}	Rat	Vapour	mg/L	
			Aerosol	mg/L	
			Gas	ppm	

Once the LD_{50} and LC_{50} values have been obtained, the GHS category can be determined from Figure 6. If the LD_{50} or LC_{50} is on a borderline, the higher toxicity category should be assigned.

5.2 MIXTURES

Under the CLP regulations, the term mixture includes any dilutions of a substance as well as several substances mixed together. If an LD_{50} or LC_{50} has been determined experimentally for a particular mixture, then this value can be used to determine the GHS classification of that mixture. Unless the mixture is used widely enough to be included in the toxicology databases described above, then it is likely that these values would be from the manufacturer. Some manufacturers may provide LD_{50}/LC_{50} values for a similar mixture instead of the mixture itself. The applicability of these values to the mixture under assessment should be assessed by a toxicology specialist as this requires expert judgement.

Additional animal testing of mixtures is expensive and is not encouraged for animal welfare reasons, so lethality data for the mixture itself or for a similar mixture are not available in the majority of cases. So, mixtures are usually classified using the 'Acute Toxicity Estimate' (ATE) approach, as described in the REACH regulation (EC, 2006). To calculate the ATE for a mixture, the same data as for pure substances (see above) will be required for each major ingredient in the mixture. 'Harmless' substances in the mixture are discounted and not considered in the equations below (harmless is defined as having an oral $LD_{50} > 2000$ mg/kg).

If less than 10% of the mixture consists of unknown components or components with unknown toxicity, then the following equation (1) (EC, 2008) should be used to determine the ATE:

$$\frac{100}{\mathrm{ATE_{mixture}}} = \sum \frac{\mathrm{C_{ingredient}}}{\mathrm{ATE_{ingredient}}} \quad (1)$$

where C is the concentration in appropriate units.

If more than 10% of the mixture consists of unknown components or components with unknown toxicity, then equation (2) (EC, 2008) should be used to determine the ATE:

$$\frac{100 - \Sigma \mathrm{C_{unknown}}}{\mathrm{ATE_{mixture}}} = \sum \frac{\mathrm{C_{ingredient}}}{\mathrm{ATE_{ingredient}}} \quad (2)$$

The ATE of an ingredient can also be estimated from its GHS classification if its LD/LC_{50} is not available, by using Table 3.1.2 in the CLP Regulation (EC, 2008). However, a significant limitation of this method is that

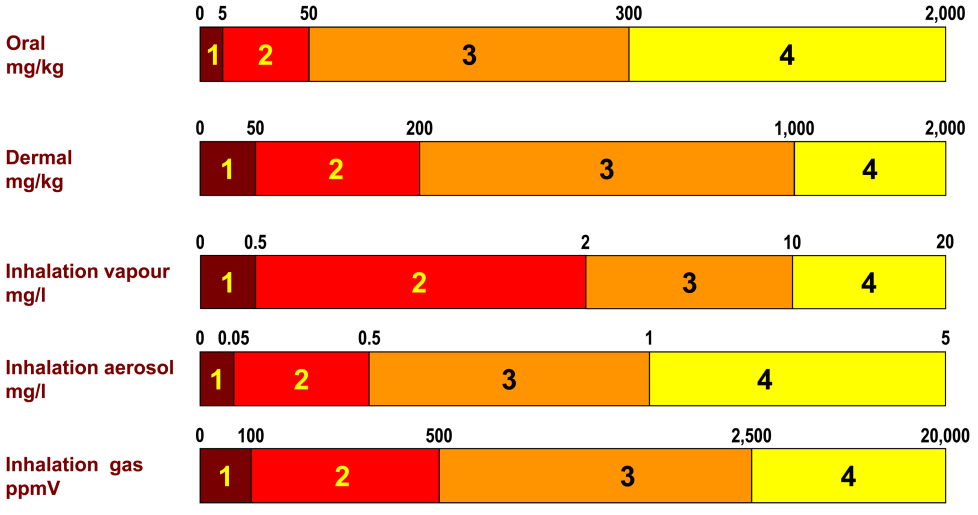

Figure 6. LD_{50} and LC_{50} ranges for different GHS categories

Table 3.1.2 provides a 'worst case' estimate of the LD/LC_{50} value (i.e. it assumes that the LD/LC_{50} value is close to the lower end of the range for each GHS classification category), which could result in the acute toxicity of the mixture being overestimated. Once an ATE for a mixture has been determined for an exposure route, it can be used to determine the GHS classification in exactly the same way as for pure substances, using the appropriate part of Figure 6 for the exposure route. As with pure substances, this would need to be done for all relevant exposure routes.

6. CONCLUSIONS

1. A key change to be introduced by the forthcoming Seveso III Directive will be the determination of the scope of the directive by means of GHS classifications of substances.
2. A survey of UK COMAH sites was carried out to obtain data to help assess the impact on the UK of the various alignment options of the Seveso Directive with GHS classifications for acute toxicity.
3. Substantial problems were found with toxicity data available in Material Safety Data Sheets (MSDS) supplied by COMAH companies for their substances and mixtures.
4. In those cases where the GHS categories of substances are not already available, MSDS data alone are unlikely to be sufficient to allow companies to determine how Seveso III will affect them.
5. Methods have been outlined for determining GHS categories for acute toxicity, using data from available toxicity databases.

Disclaimer: The opinions stated in this paper are those of the authors and do not necessarily reflect the policy of the Health and Safety Executive.

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