

Classification of Mixtures

The role of expert judgement

In Europe, there has been a general requirement for many years to label materials with suitable risk and safety phrases and to provide a safety data sheet describing the properties and risk management of the material. As part of the Global Harmonisation System (GHS) to ensure similar hazard communication around the World, Europe has introduced the Classification, Labelling and Packaging (CLP) Regulation that started to come into force from December 2010.

As well as the obvious changes in classification requirements with different coloured pictograms (or symbols) and a shift from R and S phrases to H and P statements, there is a more subtle change in the way that diluted or blended products (mixtures) need to be assessed for classification. This change from the old EU Preparations Directive to CLP is that CLP puts less emphasis on making simple calculations for mixtures of chemical substances and instead asks for greater expert judgment.

As in common with many EU regulations and guidance, the term 'expert' is not defined.

The purpose of this short report is to provide a brief outline of issues concerning the hazard assessment, classification and exposure assessment for mixtures and the reporting within the SDS.

History : Classification of preparations under Directive 1999/45/EC

The supply of mixtures of chemicals creates regulatory and practical difficulties in terms of assessing their safety. The Preparations Directive 1999/45/EC attempted to cover issues for mixtures using assumptions that diluting a hazardous component will reduce the hazard from that substance. There was also an assumption that the hazard resulting from a mixture of substances is proportional to the concentration of those substances.

This short 'historical' guide is important to understand as it sets the scene for GHS (and in Europe, CLP) and in the absence of other data, the dilution and additive effects can still be used to classify and label mixtures.

The assumptions outlined above ignored accumulative, synergistic and antagonistic effects. This was recognised in terms of physical safety such as flammability, explosivity or oxidising properties and there has been an expectation that physical hazards are assessed for mixtures. However, there has been an assumption that the toxicological properties of a mixture can be calculated from the toxicity of the components; this assumption has been largely accepted on the basis that this has the potential to reduce the need to test mixtures on animals. The knock-on advantage to industry is that this also saves costs of further testing.

The original Preparations Directive 88/379/EEC included tables and other guidance for the classification of preparations for toxicological properties. This was expanded in Directive 1999/45/EC to include environmental effects. The Directive gave examples of how to classify

and label preparations to indicate their hazard class based on acute toxicity, irritancy and acute environmental effect data as shown below. There were also defined limits for substances with other dangerous properties such as sensitising and mutagenic effects over which it was obligatory to define that component on the label.

Dilution effect tables – Directive 1999/45/EC

The tables shown below are adapted from some of those in the Preparations Directive. The function of these is to determine the classification of a preparation based on the content of a single hazardous component. Where there was more than one hazardous component, the sum of the concentrations of these would be used in making the classification.

Acute toxicity data

Substance Classification	Preparation Classification		
	Very Toxic T+ R26, 27, 28	Toxic T R23, 24, 25	Harmful Xn R20, 21, 22
Very Toxic T+ R26, 27, 28	> 7%	1 – 7%	0.1 - 1 %
Toxic T R23, 24, 25		> 25%	3 – 25%
Harmful Xn R20, 21, 22			> 25%

Irritation and Corrosive Classifications

Substance Classification	Preparation Classification		
	Corrosive C R34	Severe irritant Xi R41	Irritant Xi R36, 37, 38
Corrosive C R34	> 10%	–	5 – 10%
Severe irritant Xi R41		> 10%	5 – 10%
Irritant Xi R36, 37, 38			> 20%

Acute environmental effects

Substance Classification	Preparation Classification		
	Very toxic N R50/53	Toxic N R51/53	Harmful R52/53
Very toxic N R50/53	>25%	2.5 – 25%	0.25 – 2.5%
Toxic N R51/53		>25%	2.5 – 25%
Harmful R52/53			>25%

These generic tables were used in cases where there were no mandated 'official' dilution factors in Annex I of 67/548/EEC; the last revision of Annex I was the 31st ATP of 2009 that was immediately obsolete and became part of the 1st ATP for Annex VI of the CLP Regulation. Although many of the dilution factors in the old Annex I were carried over to Annex VI of CLP, there are now fewer and as a result, it is necessary to fall back on generic dilution factors ('levels of concern') or to use expert judgment to estimate the hazards of dilutions or mixtures. These tables were not themselves fully replaced by CLP. These are described in more detail later.

Estimating Acute Toxicity Estimate (ATE)

Due to animal welfare legislation in Europe, it is illegal for contract testing organisations to administer a chemical to an animal where it is known to cause distress. Dose levels for testing must be set at levels that do not cause distress to animals; it is obviously impossible to know what level of stress the animals are under throughout the whole procedures, but testing facilities have a legal duty to minimise this.

Unfortunately, animals are harmed and the outcome of many animal studies will include death and severe clinical signs, especially to the limited numbers of animals used in preliminary or screening studies. However, performing LD₅₀ studies has been outlawed in Europe for many years; by definition, to find a dose or concentration causing an estimated 50% mortality, it is necessary to deliberately administer dose levels above thresholds reasonably expected to cause mortality and other severe effects.

In Europe, the end-point for short-term single dose studies is the 'discriminating dose'. This is the highest concentration administered that has not caused significant effects to the animals. In repeat-dose studies, this is known as the No Observed Adverse Effect Level (NOAEL).

The LD₅₀ is still permitted in parts of the World with less regard to animal welfare and to allow harmonisation under GHS, CLP describes the 'Acute Toxicity Estimate' as a way of converting discriminating dose to the equivalent of an LD₅₀ for purposes of classification. This mechanism for conversion was also in place under earlier EU Directives.

The use of the Acute Toxicity Estimate for classification is described in Annex I of CLP, Table 3.1.1. For example, Table 3.1.1 suggests that if the Acute Toxicity (Range) Estimate is 300 – 2000 mg/kg, then Category 4 applies. This means that the discriminating dose is > 300 mg/kg and LD₅₀ is < 2000 mg/kg.

For mixtures, it gets more confusing, especially if only the Categories for classification are provided and it is not known whether this is based on a 'point' ATE (eg LD₅₀) or 'range' ATE (discriminating dose). Table 3.1.2 tries to remedy this and if the Category is known, then a fixed ATE can be used for calculation.

For example, a Category 4 acute oral substance with ATE (range) 300 – 2000 mg/kg can be assumed to have a 'point' ATE of 500 mg/kg. Therefore, if diluted to < 25%, the calculated ATE based on simple dilution is 2000 mg/kg and is therefore outside the 300 – 2000 range for classification as Cat 4. Note that this would then fall into Cat 5, if being used (early indications suggest that Cat 5 will be used by many international suppliers, even though not

part of European CLP).

This simple process of dilution to remove or reduce hazard needs to be considered with caution and interaction between components must be understood or estimated on a case-by-case basis.

Factors affecting toxicity of mixtures

Simple dilution and additivity of effects will often be valid, especially if mixing in water or with truly inert materials. However, even non-hazardous materials can interact with other components and mixtures can be more or less hazardous than estimates.

Some key properties to be aware of when predicting if simple dilution or addition is appropriate are outlined below and in most cases are the result of enhancing a substance through formulation to change the physico-chemical properties:

- Change in physical form (eg solid dissolved in liquid)
- Surface tension reduction (use of surfactants as wetting and penetration aids)
- Solvents (increased fat solubility and penetration)
- Emulsions (fatty materials dispersed finely in water)
- Solubilised metals

There are many cases of two or more substances not individually classified as hazardous being mixed together to form a hazardous mixture; in the US, it is normal to test mixtures and not the single components and this is perhaps a better option for good assessment, although it will require the use of more laboratory animals as each new formulation would need testing.

In-vitro skin and eye irritation can be performed on mixtures in Europe, but this does not always pick up synergistic or antagonistic effects seen in biological systems. However, as indicated above, testing mixtures on animals that contain substances known to be hazardous and likely to harm the animal is not permitted in Europe.

STOTs / CMRs etc

Dilution factors for acute toxicity, corrosivity and irritation and aquatic toxicity are easy to justify and the effects are generally reduced on dilution.

For substances that do not have clearly defined no-effect levels (for example, mutagens, carcinogens, sensitisers etc), then it is a bit of a guess to determine the concentration of no concern or establish a classification limit.

In practice, it is necessary to establish threshold limits to allow minor traces of substances of concern to be ignored. These are defined in Annex I of CLP and two limits are described; one is the “cut-off value” (i.e. the limit of concern) to identify the component and declare as part of the content (whether impurity or deliberately present) and the second is the “concentration limit” (the higher limit above which classification is triggered).

Declaration of content

Labels and safety data sheets need to identify any dangerous chemicals present within prescribed concentration limits. For substances, this is a simple requirement to provide the

chemical name of the substance itself if classified, but for mixtures containing diluted substances, limits are set at which the content needs to be declared.

There are therefore two concentration limits to consider; one is the concentration that will result in classification and the other is the generic cut-off value; in CLP, this is described in Annex I. Table 1.1 is particularly useful for short term toxicity, irritant or environmental toxicity. For CMRs, STOTs and sensitisers, the limit for classification is also the cut-off value (typically 0.1 % or 1%)

In the generic guide below, the % for ‘concern’ (taken in part from Table 1.1 in Annex I) and gives the concentration limit that dictates whether the component needs identifying on the label and SDS and if it is ‘contributing to potential hazard’. If these limits are exceeded, an SDS will need to be provided on request, even if the concentrations are below thresholds for classification

Category of Danger	Concern
Acute toxicity 1 – 3	0.1%
Acute toxicity 4	1%
STOT 1 or 2	1% ¹
Skin corrosion 1	1%
Skin irritation 2	1%
Skin or respiratory sensitiser	0.1%
CMR category 1a, 1b, 2	0.1%
Aquatic acute 1	0.1% ²
Aquatic chronic 1	0.1% ²
Aquatic chronic 2	1%
Aquatic chronic 3	1%
Aquatic chronic 4	1 %

¹STOTs are difficult and the No Observed Adverse Effect Levels must be considered in relation to classification limits

²Note M factor

The CLP legal text does note that these are generic, where no other factors are known that could impact on the safety of these limits.

M Factors

If a substance is classified Aquatic Acute 1 or Aquatic Chronic 1 with acute EC₅₀ < 1mg/l, a multiplication factor is added to aid classification of diluted mixtures. Very simply, if the EC₅₀ is 0.01 – 0.1 % the M factor is 10 and the level of concern is 10 times lower (ie. limit of concern becomes 0.01%). If the actual EC₅₀ and no-effect concentrations are known for a substance and the mixture is a simple dilution in water, M factors are not required and direct effect of dilution can be determined from real test data.

Dilution factors for classification in CLP

For each classification end point described in CLP, limits for classification are defined. In some cases, such as acute toxicity or irritation, limits can be set based on estimated effects of dilution, but for other endpoints such as flammability and aspiration toxicity (viscosity), there is often little option than to assess the properties of the mixture.

The table below simplifies some of the key classification endpoints described in the CLP Regulation. However, at the most basic level, consider these as dilution in water or inert material where there is no real chance of interaction between the components. If mixing with other hazardous substances or substances that could change biological properties, extra care is needed.

Category of Danger	Concentration limit for classification
Acute oral toxicity 1*	0.025%**
Acute oral toxicity 2*	0.25%
Acute oral toxicity 3*	5%
Acute oral toxicity 4*	25%
STOT 1	1%
STOT 2	10% (but needs SDS on request at 1%)
Skin corrosion 1	5% (becomes Cat 2 skin)
Skin corrosion 1	3% (becomes Cat 1 eye)
Skin corrosion 1	1% (no classification)
Skin irritation 2	10%
Skin or respiratory sensitiser	1% (but needs SDS on request at 0.1%)
CM Cat 1a, 1b	0.1%
R Cat 1a and 1b	0.3% (but needs SDS on request at 0.1%)
CM Cat 2	1% (but needs SDS on request at 0.1%)
R Cat 2	3% (but needs SDS on request at 0.1%)
Aquatic acute 1	0.1% ²
Aquatic chronic 1	0.1% ²
Aquatic chronic 2	1%
Aquatic chronic 3	10%
Aquatic chronic 4	1 %***

* Based on ATE point estimate in Table 3.1.2,

** Note that if below limit of concern of 0.1% for Cat 1, the legal text implies that substances can be ignored unless it is known to be of concern. Rather vague !

*** Consider on case-by-case, especially if potential vPvB or PBT.

Note that the text of the CLP Regulation covers this in detail and this is a summary of limited endpoints.

Physico-chemical properties

It is not possible to apply simple factors to physico-chemical properties to estimate mixtures and as testing does not involve animals, there is no legislation to prevent testing of mixtures, indeed, CLP obliges testing for physical hazard endpoints if no suitable data is available on which to base classification.

Obviously, if none of the components have hazardous properties, these can be ignored (for example, if none are considered oxidising, the mixture will not have oxidising properties). Many endpoints can be estimated; diluting ethanol to 4% in water is likely to make the mixture non-flammable (eg beer).

Some properties such as vapour pressure and partition coefficient may not necessarily be removed on mixing and estimation of interaction is difficult.

Conclusions

Although some help is provided with dilution factors and lower limits of concern, there is a need for expert judgment in classifying mixtures and many software tools need to be used with caution.