

Enforcement Issues for REACH and CLP

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Challenges for Enforcement

- Mixtures of chemicals
- Identification of chemicals present
- Use data to classify mixture
- Use classification to determine labelling requirements

Identification problems

- Known mixtures:
 - Product specification
 - MSDS

Known mixtures

- Relatively easy to confirm composition
 - But often labour intensive
 - Require bespoke methods

Unknown mixtures

- More difficult:
 - Literature searches
 - Screening methods
 - Various techniques
 - gc/ms, lc/dad, IR, UV
- Quantitation

Quantitation issues

- Methods can be difficult to validate
- Access to reference materials
- Method performance
- Critical levels

Classification

- June 1st 2015

Mixtures classified to CLP

STATUTORY INSTRUMENTS

2009 No. 716

HEALTH AND SAFETY

The Chemicals (Hazard Information and Packaging for
Supply) Regulations 2009

<i>Made - - - - -</i>	<i>16th March 2009</i>
<i>Laid before Parliament</i>	<i>16th March 2009</i>
<i>Coming into force - - -</i>	<i>6th April 2009</i>

REGULATIONS

REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 16 December 2008

on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

Classification to CLP

- Simple case
- Mixture of chemicals
- Only one classified as dangerous
- Nicotine
 - E-cigarettes
 - E-liquids

Typical products

- Mixtures of glycerol and propylene glycol with flavours and nicotine at concentrations:
 - 0 – 36 mg/ml
 - 0 – 3.6% (w/v)
 - (Rarely 7.2% w/v)

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
613-227-00-0	(±)-[(R*,R*) and (R*,S*)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran	419-600-2	99199-90-3	Skin Sens. 1 Aquatic Chronic 2	H317 H411	GHS07 GHS09 Wng	H317 H411			
613-228-00-6	(±)-(R*,S*)-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran	419-630-6	793669-26-8	Aquatic Chronic 2	H411	GHS09	H411			
613-230-00-7	florasulam (ISO); 2',6',8'-trifluoro-5-methoxy-5-triazolo [1,5-c]; pyrimidine-2-sulfonamide	—	145701-23-1	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410			
613-233-00-3	4,4'-(oxy-(bis(methylene))bis(1,3-dioxolane	423-230-7	56552-15-9	Eye Dam. 1	H318	GHS05 Dgr	H318			
614-001-00-4	nicotine (ISO); 3-(N-methyl-2-pyrrolidinyl)pyridine	200-193-3	54-11-5	Acute Tox. 1 Acute Tox. 3 * Aquatic Chronic 2	H310 H301 H411	GHS06 GHS09 Dgr	H310 H301 H411			
614-002-00-X	salts of nicotine	—	—	Acute Tox. 2 * Acute Tox. 1 Acute Tox. 2 * Aquatic Chronic 2	H330 H310 H300 H411	GHS06 GHS09 Dgr	H330 H310 H300 H411			A
614-003-00-5	strychnine	200-319-7	57-24-9	Acute Tox. 1 Acute Tox. 2 * Aquatic Acute 1 Aquatic Chronic 1	H310 H300 H400 H410	GHS06 GHS09 Dgr	H310 H300 H410			

Pure nicotine classification

- Acute oral toxicity cat 3
- Acute dermal toxicity cat 1
- Aquatic chronic cat 2

Nicotine toxicity

- 60 mg lethal dose
- Gives rise to LD50 of 1 mg/kg bw
- But evidence suggests it is not that toxic
 - Arch Toxicol (2014) 88:5-7

How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century

Bernd Mayer

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Acute Toxicity Estimate (ATE)

3.1.2. *Criteria for classification of substances as acutely toxic*

3.1.2.1. Substances can be allocated to one of four toxicity categories based on acute toxicity by the oral, dermal or inhalation route according to the numeric criteria shown in Table 3.1.1. Acute toxicity values are expressed as (approximate) LD₅₀ (oral, dermal) or LC₅₀ (inhalation) values or as acute toxicity estimates (ATE). Explanatory notes are shown following Table 3.1.1.

Table 3.1.1

Acute toxicity hazard categories and acute toxicity estimates (ATE) defining the respective categories

Exposure Route	Category 1	Category 2	Category 3	Category 4
Oral (mg/kg body-weight) See Note (a)	ATE ≤ 5	5 < ATE ≤ 50	50 < ATE ≤ 300	300 < ATE ≤ 2 000
Dermal (mg/kg bodyweight) See Note (a)	ATE ≤ 50	50 < ATE ≤ 200	200 < ATE ≤ 1 000	1 000 < ATE ≤ 2 000
Gases (ppmV ⁽¹⁾) see: Note (a) Note (b)	ATE ≤ 100	100 < ATE ≤ 500	500 < ATE ≤ 2 500	2 500 < ATE ≤ 20 000
Vapours (mg/l) see: Note (a) Note (b) Note (c)	ATE ≤ 0,5	0,5 < ATE ≤ 2,0	2,0 < ATE ≤ 10,0	10,0 < ATE ≤ 20,0
Dusts and Mists (mg/l) see: Note (a)	ATE ≤ 0,05	0,05 < ATE ≤	0,5 < ATE ≤ 1,0	1,0 < ATE ≤ 5,0

Acute Toxicity Estimate (ATE)

Exposure Route	Category 1	Category 2	Category 3
Oral (mg/kg body-weight) See Note (a)	ATE \leq 5	5 < ATE \leq 50	50 < ATE \leq 300
Dermal (mg/kg bodyweight) See Note (a)	ATE \leq 50	50 < ATE \leq 200	200 < ATE \leq 1 000

- Acute oral cat 3 implies ATE between 50 and 300 mg/kg bw
- Acute dermal cat 1 implies ATE less than 50 mg/kg bw

Acute Toxicity Estimate (ATE)

- Table 3.1.2 indicates that for ATE in the range 0 – 50 a value of 5 should be used.
- Worst case
 - Oral ATE 50
 - Dermal ATE 5

Classification!

- Formula 3.1.3.6.1

$$\frac{100}{ATE_{mit}} = \sum \frac{C_i}{n ATE_i}$$

where:

C_i = concentration of ingredient i (% w/w or % v/v)

i = the individual ingredient from 1 to n

n = the number of ingredients

ATE_i = Acute Toxicity Estimate of ingredient i .

Classification

- $ATE_{(mix)} = (100 \times ATE_{(nicotine)}) / C$
- Using $ATE_{(nicotine)}$ of 50 and nicotine concentration 2.5%
- $ATE_{(mix)} = (100 \times 50) / 2.5$
- $ATE_{(mix)} = 2000$

Classification

- ATE 2000 equates to classification:
 - **Acute oral cat 4** (from table 3.1.1)

Classification

- Using ATE of 5 for dermal toxicity
- $ATE_{(mix)} = 200$
- ATE 200 equates to classification:
 - **Acute dermal cat 3** (from table 3.1.1)

Classification

- 2.5% nicotine solution
 - **Acute oral cat 4**
 - **Acute dermal cat 3**

Environmental effects

- Table 4.1.0
- indicates aquatic chronic cat 2 = 1-10 mg/l

Environmental effects





- Summation method in 4.1.3.5.5
- nicotine cont exceeds 2.5%:
- classified as **aqu chr cat 3.**

- If less than 2.5% **aqu chr cat 4**

Labelling

Table 3.1.3

Acute toxicity label elements

Classification	Category 1	Category 2	Category 3	Category 4
GHS Pictograms				
Signal Word	Danger	Danger	Danger	Warning
Hazard Statement: — Oral	H300: Fatal if swal- lowed	H300: Fatal if swal- lowed	H301: Toxic if swal- lowed	H302: Harmful if swal- lowed
— Dermal	H310: Fatal in contact with skin	H310: Fatal in contact with skin	H311: Toxic in contact with skin	H312: Harmful in contact with skin

labelling

- Table 3.1.3 gives:
- Warning symbols
- Hazard statements
- Precautionary statements

Classification dependant on ATE value

		oral toxicity		dermal toxicity
mg/ml	%	ATE = 1 class	ATE = 50 class	ATE = 5 class
0	0	n/c	n/c	n/c
6	0.6	cat3 oral	n/c	cat3 dermal
12	1.2	cat3 oral	n/c	cat3 dermal
25	2.5	cat2 oral	cat4 oral	cat3 dermal
70	7	cat2 oral	cat4 oral	cat2 dermal

Labelling

Maximum of 6 P statements normally

Cat 4 oral, cat 2 dermal requirements (above 2.5%)

Signal word
Pictograms

DANGER



Hazard and Precautionary statements;

H301	Harmful if swallowed
H311	Fatal in contact with skin.
H412	Harmful to aquatic life with long lasting effects.
P405	Store locked up.
P102	Keep out of reach of children
P103	Read label before use.
P264	Wash hands thoroughly after handling
P280	Wear protective gloves
P301+P312	IF SWALLOWED: Call a POISON CENTER or doctor/physician if you feel unwell
P302 + P350	IF ON SKIN: Gently wash with plenty of soap and water
P273	Avoid release to the environment.

CAT 3 toxicity requires child-resistant closure

Tactile warning required

Labelling

Cat 4 oral, cat 3 dermal requirements (2.5% or less)

Signal word WARNING

Pictograms



Hazard and Precautionary statements;

H302	Harmful if swallowed
H312	Harmful in contact with skin.
H413	May cause long lasting harmful effects to aquatic life
P405	Store locked up.
P102	Keep out of reach of children
P103	Read label before use.
P280	Wear protective gloves
P301+P312	IF SWALLOWED: Call a POISON CENTER or doctor/physician if you feel unwell
P302 + P352	IF ON SKIN: Wash with plenty of soap and water
P273	Avoid release to the environment.

CAT 4 toxicity requires child-resistant closure
Tactile warning required

Thanks!

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