Practical Guide for Mixtures and LCID Methodology – Progress Report

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cefic

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Background

Safe use of (substances in) mixtures

How to use ES information for the safe use of mixtures

Lot of challenges

CSR/ES Roadmap

Action area 4 : Support to formulators

Action 4.1 Action 4.2 Action 4.3

Action 4.4 Action 4.5 Action 4.6

Action 4.4.A Action 4.4.B

Practical solutions are being developed

A bit of history …

Presented several approaches being developed

Presented results mapping exercise

Interim reporting on LCID Method

Presented draft LCID methodology

Presenting outcome consultation

ENES 4 | **ENES 5** | **ENES 6** | **ENES 7** | **ENES 8**

2013 | 2014 | 2015

- Mapping available approaches to generate safe use info for mixtures
- 2 main approaches
  - Generally applicable (top down)
  - Sector-specific (bottom up)

CSR/ES Roadmap **Action 4.4.A**

Development of common concept for a top down methodology **LCID methodology**

Consultation on LCID methodology

Both approaches are complementary to each other

Bottom up approaches are further developed by sector associations - working together to:

- Exchange experiences
- Find harmonised solutions for similar challenges
- Align as much as possible sector-specific methodologies
- Agree on terminology

CSR/ES Roadmap **Action 4.4.B**

Agenda

1. Comments received
2. Examples
3. Round Robin testing
4. Next steps

Thank you

General comments

From ENES7 received feedback:

11 **Contributors**

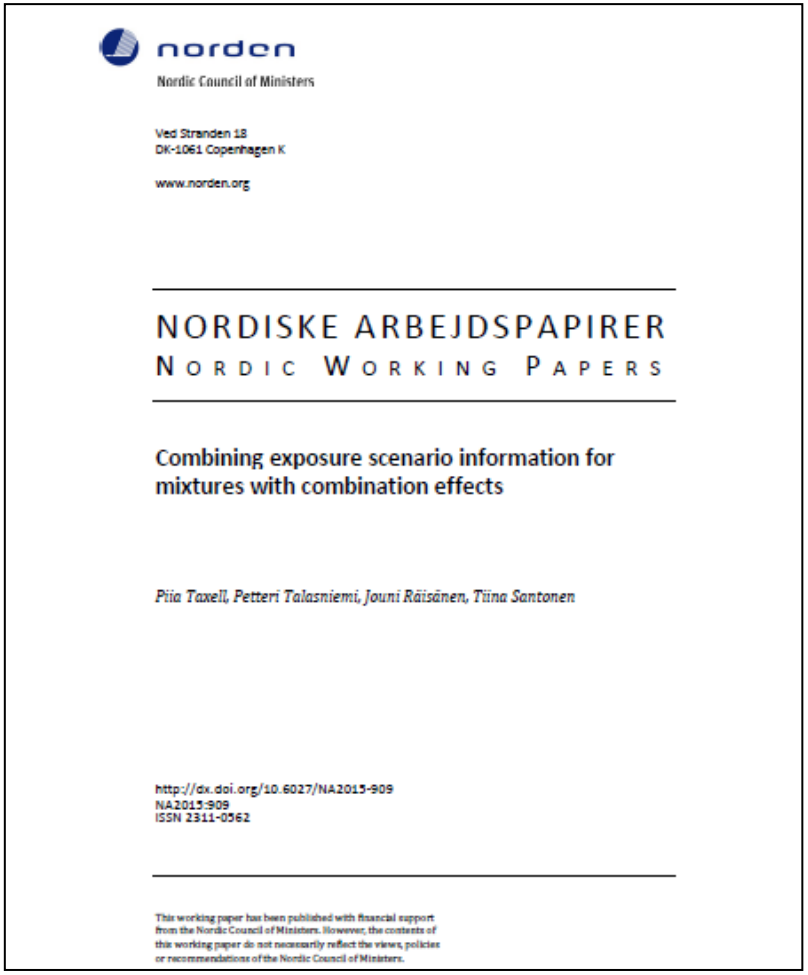
140 **Comments**

- **Overall supportive of structure and content**
- **Seek clarification and further elaboration of workflow**

Comments


Companies
Competent Authorities
Trade Associations
ECHA

Nordic working paper



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Combining exposure scenario information for mixtures with combination effects

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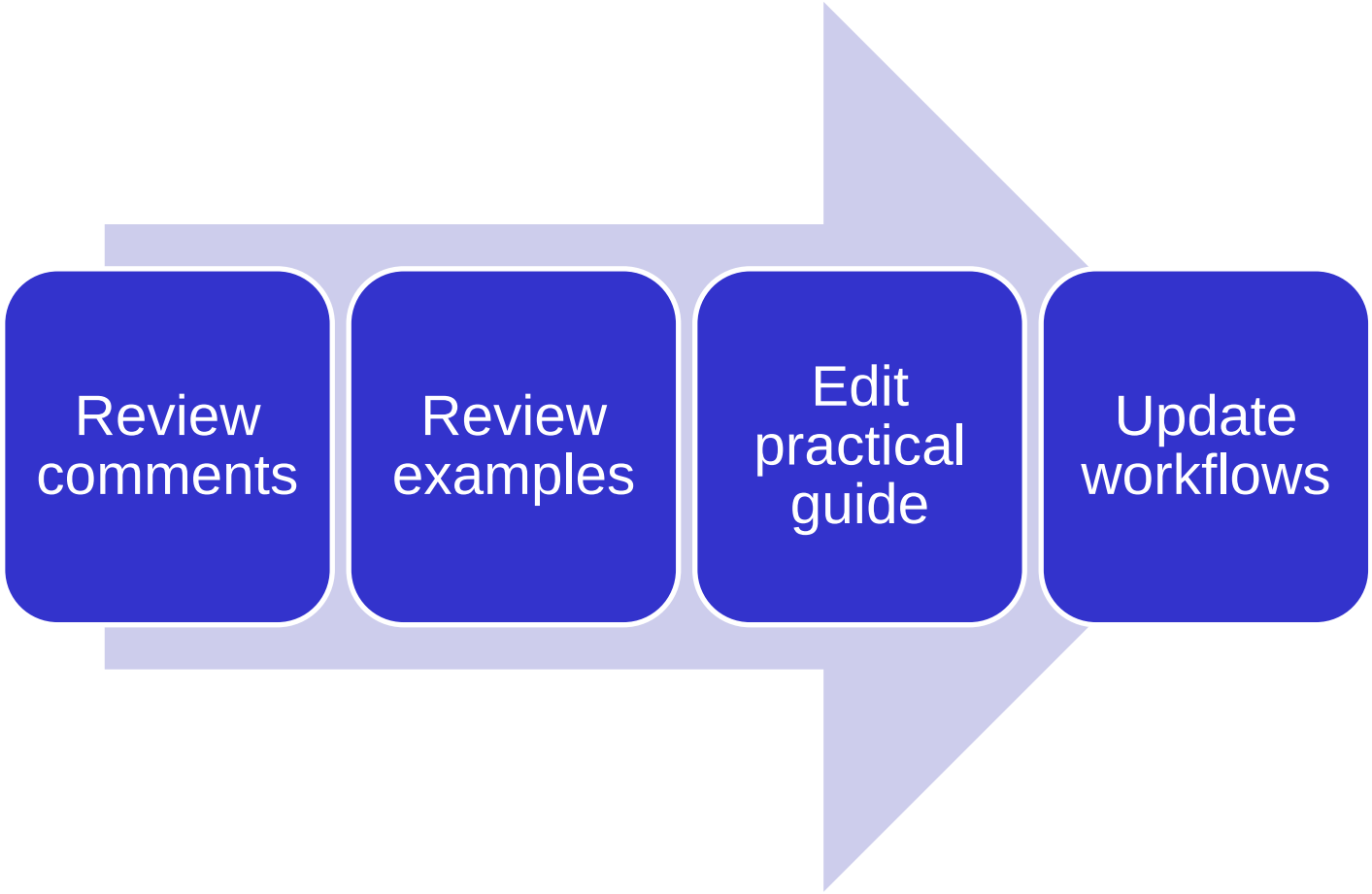
- Recently received comments
- Addressing a few of the issues herein
- Will follow-up once able to review more extensively

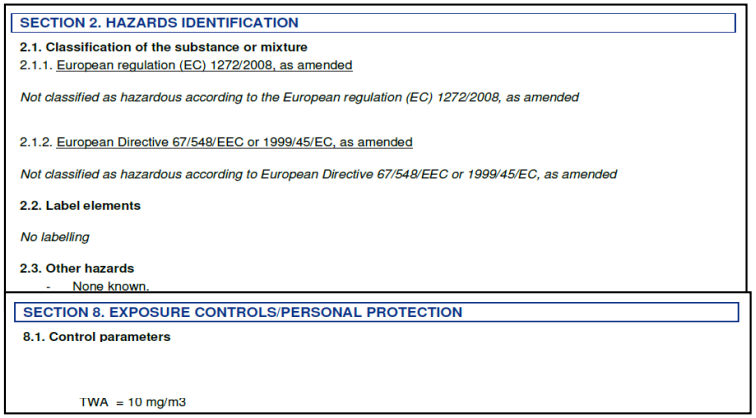
Process


Review comments
Review examples
Edit practical guide
Update workflows

General comments

Terms Definitions	Non-Classified Mixtures	Figures	SDS Examples	Round Robin Testing
• Clarifications • Amendments • Consistency checks	• Address in workflow	• Consistency	• Under consideration	• Check reproducibility of LCID

Addressing non-classified mixtures



SECTION 2. HAZARDS IDENTIFICATION

2.1. Classification of the substance or mixture

2.1.1. European regulation (EC) 1272/2008, as amended

Not classified as hazardous according to the European regulation (EC) 1272/2008, as amended

2.1.2. European Directive 67/548/EEC or 1999/45/EC, as amended

Not classified as hazardous according to European Directive 67/548/EEC or 1999/45/EC, as amended

2.2. Label elements

No labelling

2.3. Other hazards

- None known.

SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

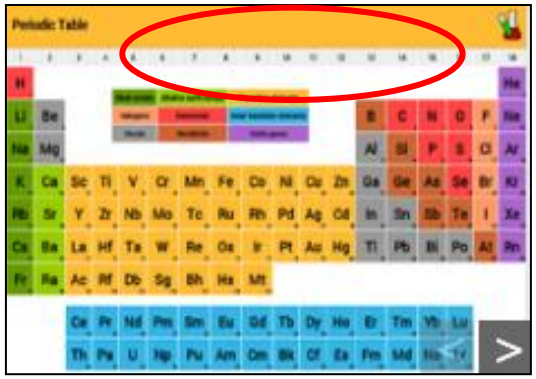
8.1. Control parameters

TWA = 10 mg/m3

- LCID may be applied for unclassified mixtures
- Assume when classifying the mixture, consideration was made based on experience and knowledge, e.g., exposures occur above OELs despite low concentrations
- LCID will not cover 100% of cases; the last step asks to review the outcome and, if necessary, apply expert judgement to revise/refine results
- SDS is required for classified mixtures and LCID methodology will cover most of these cases

Metals

- Added massives/solids to scope
- Need to provide examples



Priority substances further defined

Carcinogens, mutagens, Persistent, Bioaccumulative Toxic substances (PBTs), and very Persistent and very Bioaccumulative substances (vPvBs) are:

- Generally assumed to have the most stringent Risk Management Measures
- Usually don't have DNELs
- This is not necessarily the same for reproductive toxicants

Carcinogen, Categories 1A, 1B or 2
Mutagen, Categories 1A, 1B or 2
PBTs and vPvBs

Control steps now part of HH workflow

Step 2 Compiling REACH-relevant data	• Include internal documentation and/or experience
Step H5a Identify OCs and RMMs for Priority Substances	• If only protective for one route of exposure, consider LCI calculations for other routes
Step H6 Identify relevant components	• Ensure hazard classifications align with Section 2 of SDS; include components that contribute even if below concentration cut-offs

Control steps now part of ENV workflow

Step E15

Compiling OCs and RMMs

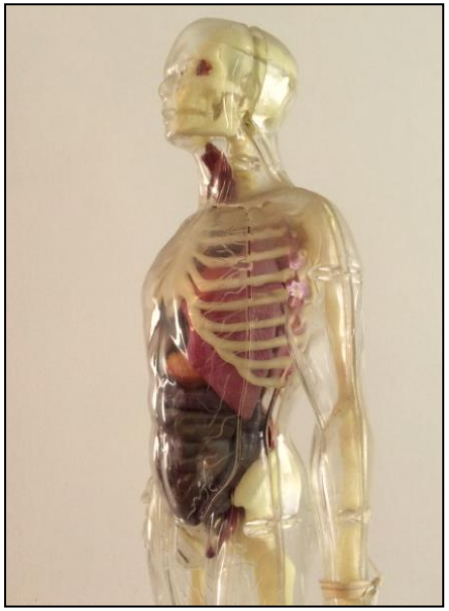
- Ensure final RMMs cover:
  - Possible hazards, if any, from components below CLP thresholds
  - All possible release pathways
  - Is not substance-specific

Clarified choice of DNELs

- Identify all components that add to the systemic effects of the mixture (i.e., those classified for acute toxicity, reproductive toxicity and Specific Target Organ Toxicity Single / Repeated exposure (STOT-SE/STOT-RE, Cat. 1+2)

- These are the ones relevant for the DNEL-based calculations

- Local effects covered separately



Local effects clarified

- Eye, skin, or respiratory tract irritation/corrosivity
- Skin or respiratory sensitization
- STOT-SE Category 3 effects, such as drowsiness and dizziness
- EUH066, dryness or cracking of the skin . . . . .

Incorporating RMMs for local effects

LCI (DNEL) - inh	60 / 2 = 30	19 / 10 = 1.9	21/10 = 2.1
LCI (DNEL) - derm	N/A	19 /30 = 0.63	21/50 = 0.42
LCI (DNEL) - oral	N/A	N/A	
Highlight Lead Component (LC) - inhalation	Lead Component for inhalation exposure route	Lead Component for dermal exposure route	
Relevant local effects	Skin corr. 1A	None	STOT SE 3 May cause drowsiness or dizziness.
Exposure Scenario			
Contributing Scenario			
Operating Conditions (OCs)	**Indoor** **5 days per week; < 4h per day**	**Indoor** **5 days per week; < 4h per day**	**Indoor** **5 days per week; < 4h per day**
Risk Management Measures (RMMs)	**Good general ventilation** **Gloves tested to EN 374** **Suitable working clothes**	Good general ventilation **Gloves tested to EN 374**	**Local exhaust ventilation** Gloves tested to EN 374
Modified OCs for the Mixture	**Indoor; 5 days per week; < 4h per day**		
Modified RMMs for the Mixture	**Local exhaust ventilation** **Gloves tested to EN 374** **Suitable working clothes**		

Component 1: LC inhalation & local effects, skin corrosivity

Component 2: LC dermal; Component 3: narcotic effects

RMM:

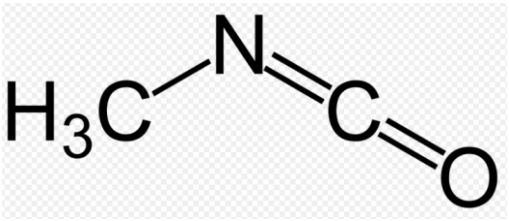
Component 1: Gloves and Suitable working clothes;

Component 2: Gloves; Component 3: Local exhaust ventilation (which supercedes Good general ventilation from Comp. 1)

Apply bridging principles for surrogates

An assessment may also be based on data from a reasonably similar composition or a “surrogate mixture,” i.e., a mixture close in composition to the mixture under evaluation **(see ECHA Guidance on CLP for details on bridging principles)**.

Definition of grouping updated



Grouping may be considered if there are components in the mixture of similar structure and are known to have similar toxicological effects via similar modes of action, for example, isocyanates or acetic anhydrides.

At present, the LCID methodology does follow the hazard additivity principles utilized for CLP classifications (ECHA, 2013)*

* ECHA, Guidance on the Application of the CLP Criteria, Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, 2013

$C_{weighted}$ formula

$$C_{weighted} = \sum_{i=1}^{n} \frac{C_i \times DNEL_{LC}}{DNEL_i}$$

Where:
C_i: Concentration of the components from the group identified under Step H10 for a given exposure route
$DNEL_{LC}$: DNEL of the Lead Component
$DNEL_i$: DNEL of the components from the group identified under Step H1 for a given exposure route

- **Formula aligns with "like" calculation for the environment**
- **Vapour pressures not included in the calculation; VP only relevant when considering exposure potential; doesn't impact the overall toxicity of the components**

Distinguish back-up approach results

Lead Component Candidate Indicator

LCCI

$$LCCI_{\alpha} = \frac{C_i}{NO(A)EL/NO(A)EC} \qquad LCCI_{\alpha} = \frac{C_i}{LD50/LC50/\ ATE}$$

Introduced new term to differentiate between indicators based on DNELs-LCIs vs those based on alternatives, e.g., NO(AELs)-LCCI

Bioavailability is not needed to identify Lead Component

Bioavailability, partition coefficients are relevant for an environmental exposure assessment, but not necessary to identify the Lead Component

The LCID methodology is based on the principle that if the risks are controlled for the most hazardous component, then the risks from the other substances in the mixture are also controlled.

Environmental compartments

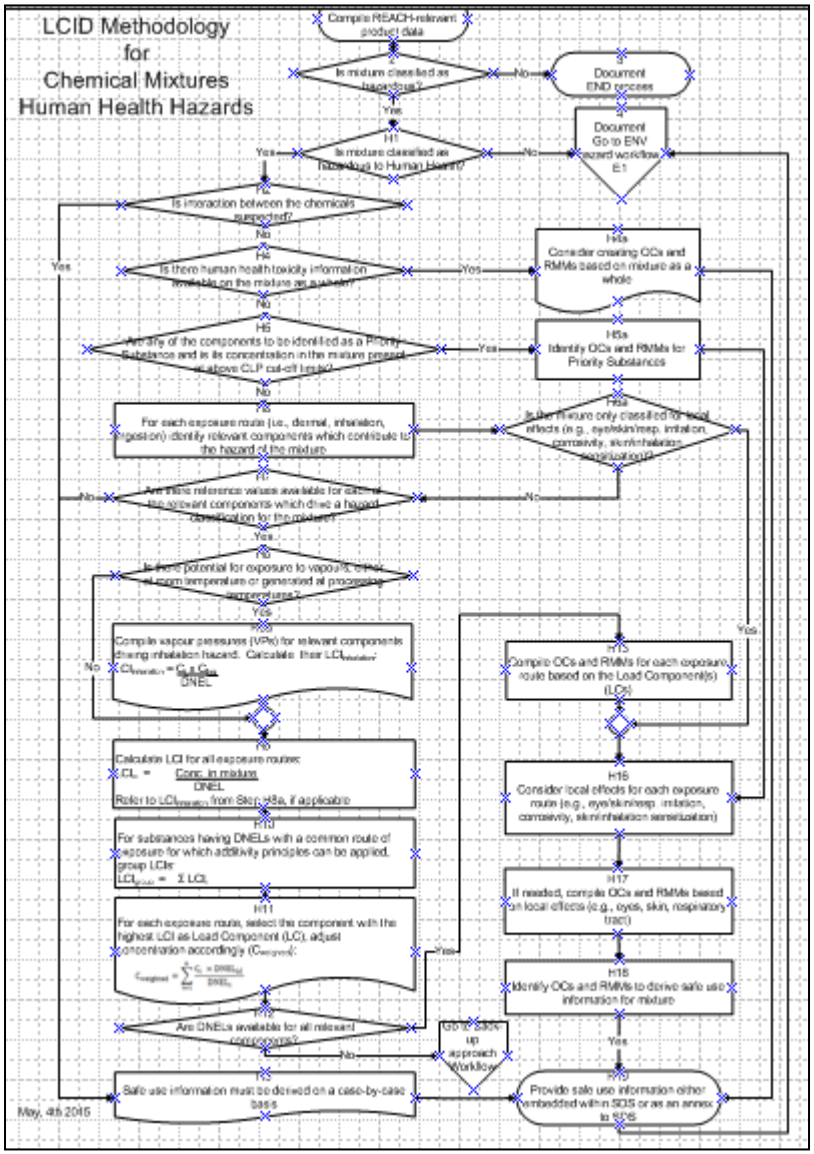
- "Hazardous to the ozone layer" is dealt separately.
- The most critical RCR of all compartments feeds into the calculation of the Lead Component; therefore, in a way, all compartments are considered.
- Last step addresses if Lead Component identified is providing safety control measures for only one release route then others need to be considered.

M_{safe} not available?

- Consider contacting supplier
- However, derivation of safe use information for the mixture can be done without component M_{safe}s
- A conservative surrogate for M_{safe} could be the daily amount used at a site (as stated by the supplier) or

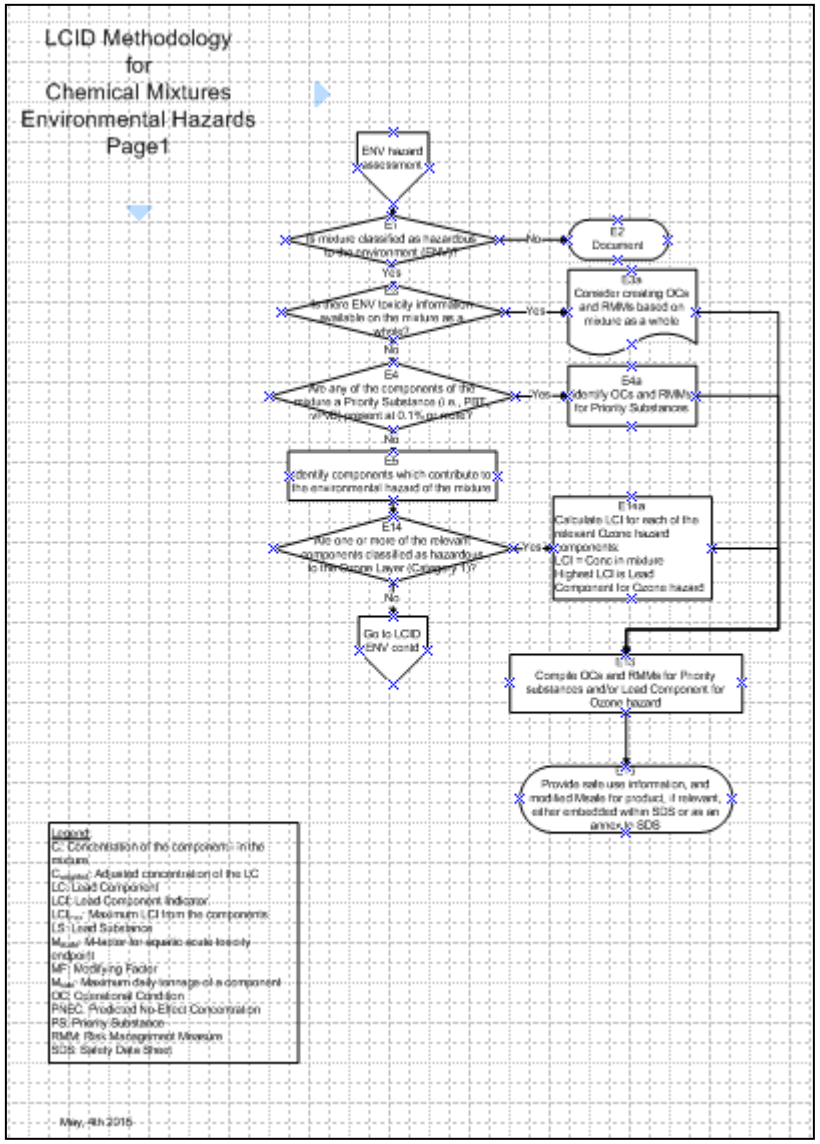
$$\text{Daily amt at site} = \frac{\text{Annual amt used at site}}{\text{emission days}}$$

LCID human health hazard workflow



- Added step if only classified having local effects, one can skip LCI calculations
- To be more legible now two pages
- Second page addresses back-up calculations
- Added a legend
- More user-friendly

LCID environmental hazard workflow



- Addressing presence of ozone layer hazard higher up in process
- Made into two pages
- Second page addresses back-up calculations if PNECs not available
- Added a legend
- More user-friendly

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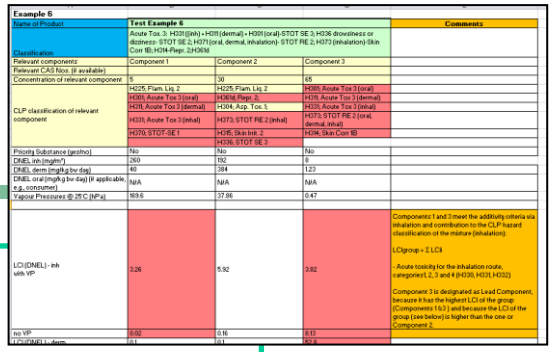
Examples



Example 6

Name of Product	Test Example 6			Comments
Classification	Acute Tox. 3; H331 (inh) - H311 (dermal) - H301 (oral)-STOT SE 3; H336 drowsiness or dizziness- STOT SE 2; H371 (oral, dermal, inhalation)- STOT RE 2; H373 (inhalation) Skin Corr 1B; H314-Repr. 2;H361d			
Relevant components	Component 1	Component 2	Component 3	
Relevant CAS Nos. (if available)				
Concentration of relevant component	5	30	65	
CLP classification of relevant component	H225; Flam. Liq. 2 H361; Acute Tox 3 (oral) H311; Acute Tox 3 (dermal) H331; Acute Tox 3 (inhal) H370; STOT-SE 1	H225; Flam. Liq. 2 H314; Repr. 2; H304; Asp. Tox. 1; H373; STOT RE 2 (inhal) H315; Skin Irrit. 2 H336; STOT SE 3	H361; Acute Tox 3 (oral) H311; Acute Tox 3 (dermal) H331; Acute Tox 3 (inhal) H373; STOT RE 2 (oral, dermal, inhal) H314; Skin Corr 1B	
Priority Substance (yes/no)	No	No	No	
DNEL inh (mg/m³)	260	192	8	
DNEL derm (mg/kg bw day)	40	384	123	
DNEL oral (mg/kg bw day) (if applicable, e.g., consumer)	N/A	N/A	N/A	
Vapour Pressure @ 25 C (kPa)	169.6	37.86	0.47	
LCI (DNEL) - inh with VP	3.26	5.92	3.82	Components 1 and 3 meet the additivity criteria via inhalation and contribution to the CLP hazard classification of the mixture (inhalation): LCIgroup = Σ LCIi - Acute toxicity for the inhalation route, categories1, 2, 3 and 4 (H330, H331,H332) Component 3 is designated as Lead Component, because it has the highest LCI of the group (Components1 to 3) and because the LCI of the group (see below) is higher than the one or Component 2.
no VP	0.02	0.16	0.13	
LCI (DNEL) - derm	0.1	0.1	0.3	

- Received very few
- Most were focused on questions/issues with the LCID tool
- Others had missing data or methodology was conducted incorrectly
- Remaining were really not much different than existing examples
- In the end, added only one more which represented a mixture of solvents and applying grouping principles

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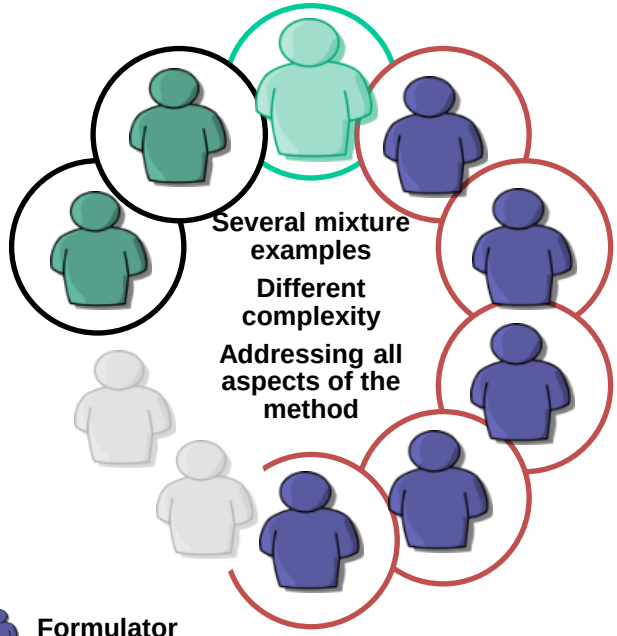
Round Robin testing of LCID

- **Objective:**
  - **Is outcome of the LCID reproducible, independent from user?**
  - **Is the LCID guide sufficiently elaborated to enable the user to apply the methodology in an appropriate way?**

- **How?**
  - **Different people apply the LCID methodology independent from each other for the same cases.**

Set up test

Test panel



Formulator

MSCA

ECHA

Mixture TF

Volunteers needed!!!

Test process

06/2015

Make available to test panel:
- Updated draft LCID practical guide
- Updated LCID calculation tool + instructions
- Report template
- Test examples

07-08 2015

Testing period

Q 3 2015

Assessing results

Results aligned?

yes

no

Detailed assessment

Amendment LCID / guide necessary?

no

yes

Amend LCID / guide accordingly

Publish guide

Q4 2015

Who wants to be part of the test panel?

- Invitation to participate will be sent to ENES 8 participants
- Volunteers can respond until mid-June
- Expected workload = max 2 days:
  - 1 day to get familiar with the method + tool, and
  - 1 day to apply the method on the examples
- Testing the method now will save you time later

Agenda

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Next steps

- Finalize assessment of comments and examples
- Finalize flowcharts
- Give feedback on comments to commenters
- Finalize update of draft Practical Guide
- Follow-up activities on tool
- Run Round Robin testing
- Develop communication plan
- Publish documents on the internet

Questions