Lead substance identification: "CLPplus" by BASF

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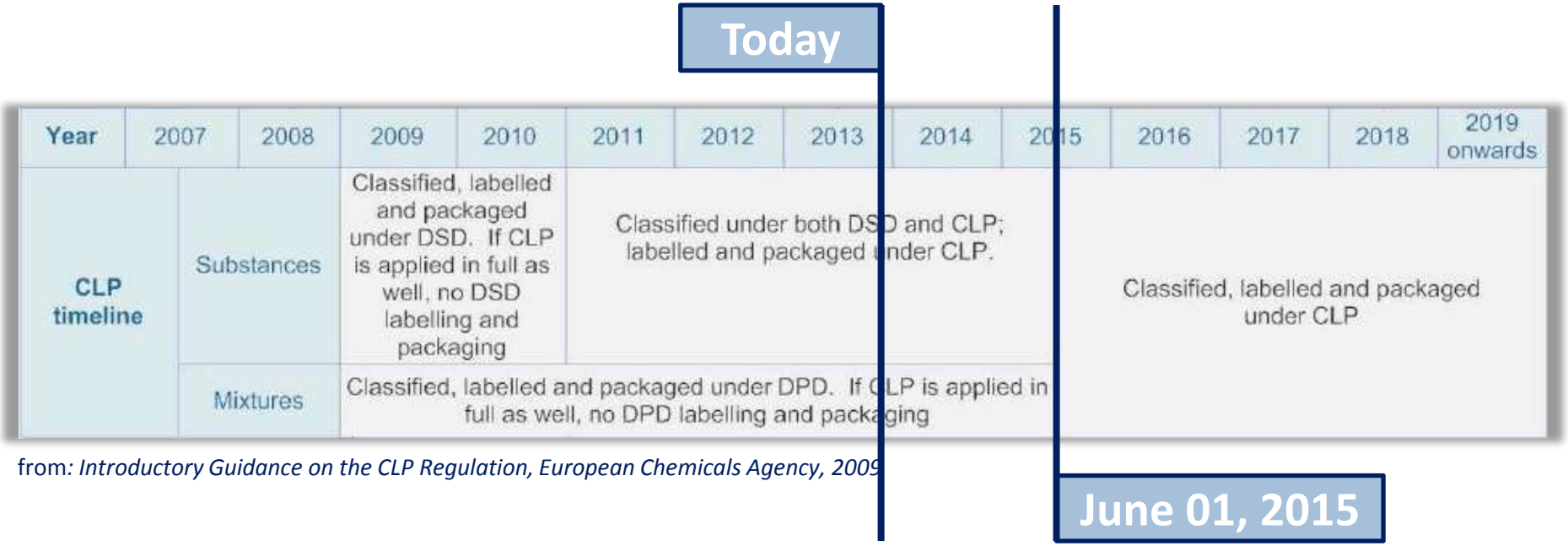
Exposure information for mixtures: the DPD plus method

- Determination of so-called "Lead substance(s)":
  - Inhalation, Dermal, Eye, Oral, Environment
  - Expo info for mixture is based on ES from Lead substance(s) only
- based on **D**angerous **P**reparations **D**irective, 1999/45/EU

Changeover to "CLPplus" required

- Timelines for CLP-Regulation (EC) No 1272/2008:



from: *Introductory Guidance on the CLP Regulation, European Chemicals Agency, 2009*

Priority substances

- Like "DPD plus", also "CLP plus" is not applicable for **priority substances**
- Hence, substances which are classified as **category 1 or 2 carcinogenic**, **category 1 or 2 mutagenic**, or which are **identified PBT**-, or **vPvB-substances**, are beyond the scope of the CLPplus-method.
- Preparations containing safety-relevant concentrations of such substances will require an **advanced evaluation**.
- Usually, products containing priority substances will require the **same safety measures** as the pure priority substance.
- Substances that are classified as **reprotoxic**, however, are part of the Lead substance identification according to the CLP plus method.

Human health: preface

- Only those components, which contribute to the classification of the mixture, are considered in the identification of the Lead substance(s).
- Lead substances are identified separately for each route of exposure. Only the relevant DNELs (long-term systemic) for each route are used in the calculation. Furthermore, LD/LC50/ATE values are only used, if the substance has been classified for the corresponding exposure pathway.

Human health approach: overview

DNELs for all compounds

Case I: DNEL approach

DNELs for some compounds

Case II

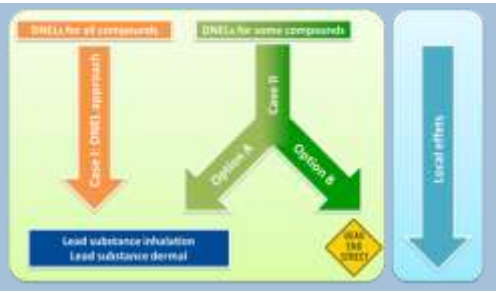
Option A

Option B

Lead substance inhalation
Lead substance dermal

Local effets

Human Health: DNEL approach



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Case I

!! Prerequisite !!

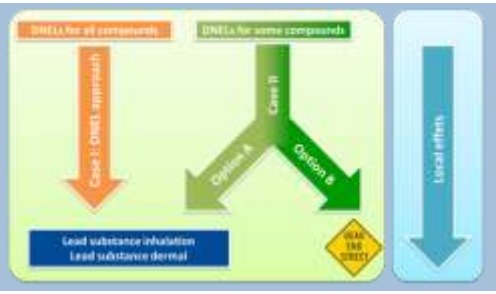
DNELs are **available** for **ALL** relevant compounds

- Per compound:

$$\text{Lead Substance Indicator (LSI)} = \frac{\text{Concentration in mixture}}{\text{DNEL}_{\text{longterm systemic}}}$$

- **Substance with highest LSI = Lead substance Human Health (to be identified per pathway)**

Human Health: surrogate approach



Case II

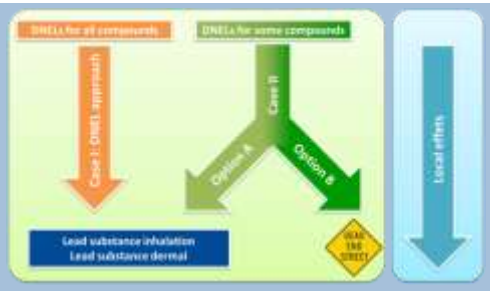
DNELs are **available** for **SOME** of the relevant compounds only

- Per compound: identify most toxic ingredient based on acute toxicity data

Lead Substance **C**andidate Indicator (LSCI) = $\frac{\text{Concentration in mixture}}{LD_{50}\text{ , }LC_{50}\text{ or ATE}}$

- **Substance with highest LSCI = Lead substance candidate Human Health (to be identified per pathway)**

Human Health: surrogate approach
Option A



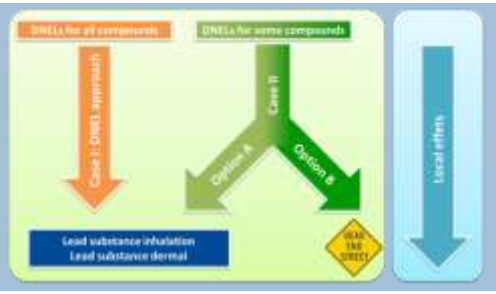
Case II (continued)

DNELs are available for SOME of the relevant compounds only

Option A: Lead substance candidate is a compound that carries DNELs

- Presumably, DNELs still to be provided (for substances with no DNELs so far) are less severe than the one of the Lead substance candidate. Therefore, measures to ensure safe use of the Lead substance candidate will likely also cover the risk by the "no-DNEL-substances".
- By applying the equation of **Case I** to all compounds for which DNELs are available, the Lead Substance is identified (per pathway). This may be – but is not necessarily – the Lead Substance candidate.

Human Health: surrogate approach
Option B



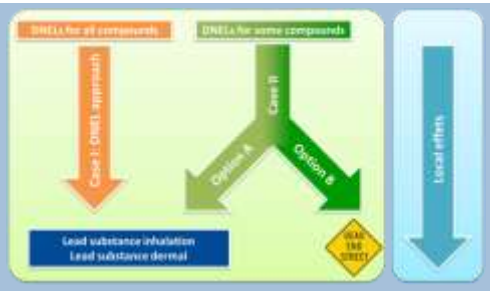
Case II (continued)

DNELs are available for SOME of the relevant compounds only

Option B: No DNELs has been derived for Lead substance candidate yet

- It has to be assumed that the Lead substance candidate drives the risk of the mixture.
- For substances without DNEL, no exposure scenarios are available. Therefore, there is also no starting point to derive safe use information for the mixture.
- Using the substance with the second highest LSCI would likely underestimate the risk of the mixture.
- **Therefore, LSI approach can´t be used in this situation**

Human Health: local effects



- **Local effects**

  Corrosive, irritating and sensitizing properties of compounds are considered concomitantly

- Eye irritating compound in mixture => goggles
- Irritating to skin and/or sensitizing agent => list compounds and call for appropriate glove(s), order of appearance defined by

$$\frac{\text{Concentration in mixture}}{\text{spec./ generic conc. limit}}$$

- Respiratory irritating compounds and respiratory sensitizers => measures from compound also apply to mixture – if not already covered by Lead Substance inhalation

Example Case I, INHALATION

Mixture classified as acute tox. (o, d, i) 3, STOT RE 1, Eye irr. 2

Comp	Classification	Conc [%]	DNEL [mg/m³]	LC50 [mg/L)
A	Eye 2, STOT RE 2	45	305	not class.
B	Acute tox. (o, d, i) 3, STOT RE 1	51	260	3
C	Acute tox. (o) 4, Eye 2, STOT SE 3 (irr.)	3	150	not class.

Comp	local effects
A	not class
B	not class
C	not cons

(as LS inhal available)

Comp	LSI
A	0.1475
B	0.1961
C	0.02

Example Case I, DERMAL

Mixture classified as acute tox. (o, d, i) 3, STOT RE 1, Eye irr. 2

Comp	Classification	Conc [%]	DNEL [mg/kg]	LC50 [mg/kg]
A	Eye 2, STOT RE 2	45	44	not class.
B	Acute tox. (o, d, i) 3, STOT RE 1	51	40	300
C	Acute tox. (o) 4, Eye 2, STOT SE 3 (irr.)	3	25	not class.

Comp	local effects
A	Eye irritant
B	not class
C	Eye irritant

Comp	LSI
A	1.0227
B	1.275
C	0.12

Example Case I, RESULT

Mixture classified as acute tox. (o, d, i) 3, STOT RE 1, Eye irr. 2

- Compound B is Lead Substance for both the inhalation as well as for the dermal path
  - based on DNEL approach

- Measures to prevent eye irritancy provided in SDSs of compounds A and C need to be considered for the product
  - based on local effects approach

Example Case II, INHALATION

Mixture classified as acute tox. inhal. 2, 3, STOT RE 2, Eye irr. 2

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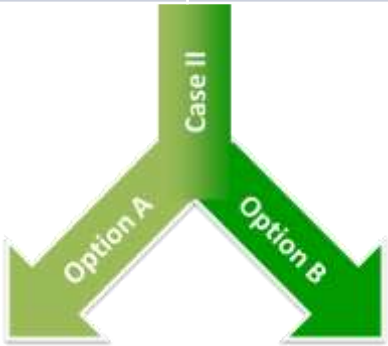
Comp	Classification	Conc [%]	DNEL [mg/m³]	LC50 [mg/L]
A	Eye 2, STOT RE 2, acute tox. (d, i) 3	30	305	4
B	Acute tox. dermal 4, Acute tox. inhal. 1	30	not avail.	0.2
Water	not classified	40	--	--

Comp	local effects
A	not class
B	not class
Water	--

Comp	LSI (DNEL)
A	0.1
B	n.a.
Water	--



Comp	LSCI (acute)
A	7.5
B	150
Water	--

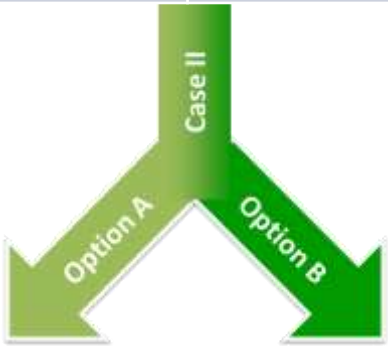
Example Case II, DERMAL

Mixture classified as acute tox. inhal. 2, 3, STOT RE 2, Eye irr. 2

Comp	Classification	Conc [%]	DNEL [mg/m³]	LC50 [mg/L]
A	Eye 2, STOT RE 2, acute tox. (d, i) 3	30	44	300
B	Acute tox. dermal 4, Acute tox. inhal. 1	30	not avail.	1500
Water	not classified	40	--	--

Comp	local effects
A	Eye irritant
B	not class
Water	--

Comp	LSI (DNEL)
A	0.68
B	n.a.
Water	--



Comp	LSCI (acute)
A	0.1
B	0.02
Water	--

Example Case II, RESULT

Mixture classified as acute tox. (o, d, i) 3, STOT RE 1, Eye irr. 2

- Compound A has highest LSCI for the dermal route. In addition, also DNELs are available for compound A. Therefore, (dermal) assessment of the mixture may be based on compound A. However…

- … compound B has highest LSCI for inhalation. But: there are no DNELs available for B. Therefore, no LS-based exposure information for the mixture can be compiled.

- (Measures to prevent eye irritancy provided in SDSs of compound A need to be considered for the product
  - based on local effects approach)

Environment: PNEC approach

- Per component:
  select **lowest PNEC** of all compartments (disregard units)
- Per component:
  Lead **S**ubstance **I**ndicator (LSI) = **Concentration in mixture / lowest PNEC**
- **Substance with highest LSI = Lead substance environment**

- *The PNEC approach is only applicable for mixtures, where PNECs are available for **ALL** ingredients which are classified as hazardous to the environment*
- *Otherwise, the classification approach should be used (see next page)*

Environment: classification approach

Classification	Calculation of LSI (Lead Substance Indicator)
Aquatic Acute 1	Concentration in mixture x M_{acute} x 33
Aquatic Chronic 1	Concentration in mixture x $M_{chronic}$ x 100
Aquatic Chronic 2	Concentration in mixture x 10
Aquatic Chronic 3	Concentration in mixture
Aquatic Chronic 4	Concentration in mixture

- Substances classified for acute and chronic hazard: **LSI_{total}** = LSI_{acute} + $LSI_{chronic}$
- **Substance with highest LSI = Lead substance environment**

Environment: CLPplus vs DPDplus

LSI DPDplus	Classification
C_i / (0.25% x 3*)	R50
C_i / 0.25%	R50/53
C_i / 2.5%	R51/53
C_i / 25%	R52/53
C_i / 25%	R53

Classification	LSI CLPplus
Aquatic Acute 1	$C_i \times M_{acute} \times 33$
Aquatic Chronic 1	$C_i \times M_{chronic} \times 100$
Aquatic Chronic 2	$C_i \times 10$
Aquatic Chronic 3	C_i
Aquatic Chronic 4	C_i

- C_i = concentration of substance in mixture
- *correction factor of 3:
  in order to reflect increased removal efficiency of R50 vs R50/53 substances

Example: environment

DPDplus

1	2	3	16	17	18
Substance *(Col H)*	Conc'n in prep *(Col F) (%)*	Vapour press *(Col G) (hPa)*	Aquatic		
			R phrase (s) *(Col J)*	Conc'n limit *(Col K or M) (%)*	LSI *[Col 2/Col 14; If R50:Col 2/ (3 X Col 17)]*
Ethyl Acetate	30.0	103			
Cyclo-hexane	30.0	104	R50/53	0.25	120
n-Hexane (Annex 1)	2.5	160	R51/53	2.5	1
Naphtha	20.0	120	R51/53	2.5	8
hydrotreated light					
Rosin	0.5	$< 10^{-6}$	-	-	-
Polychlorobutiene	17	$< 10^{-6}$	-	-	-

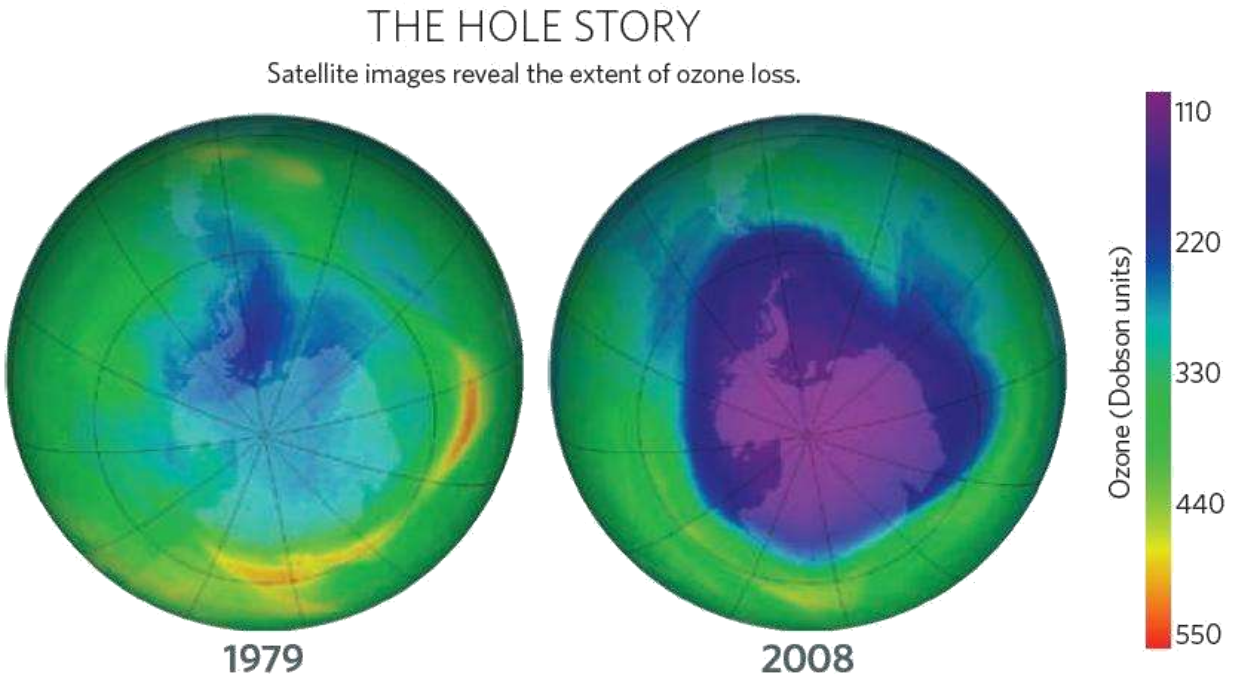
CLPplus

classification	M factor	LSI
Acute 1	1	990
Chronic 1	1	3000
		3990
Chronic 2	n.a.	**25**
Chronic 2	n.a	**200**

taken from: *DPDplus methodology, Table 3.1: determination of lead substance(s) - Example: Contact adhesive*

Components classified as hazardous to the ozone layer

- Components classified as hazardous to the ozone layer category 1:
  LSI = Concentration in mixture
- **Substance with highest LSI = Lead substance ozone layer**



Challenge:
from Lead substance to product MSDS

LS info → Adaptation → MSDS product

Exposure scenario information of Lead Substance (LS)

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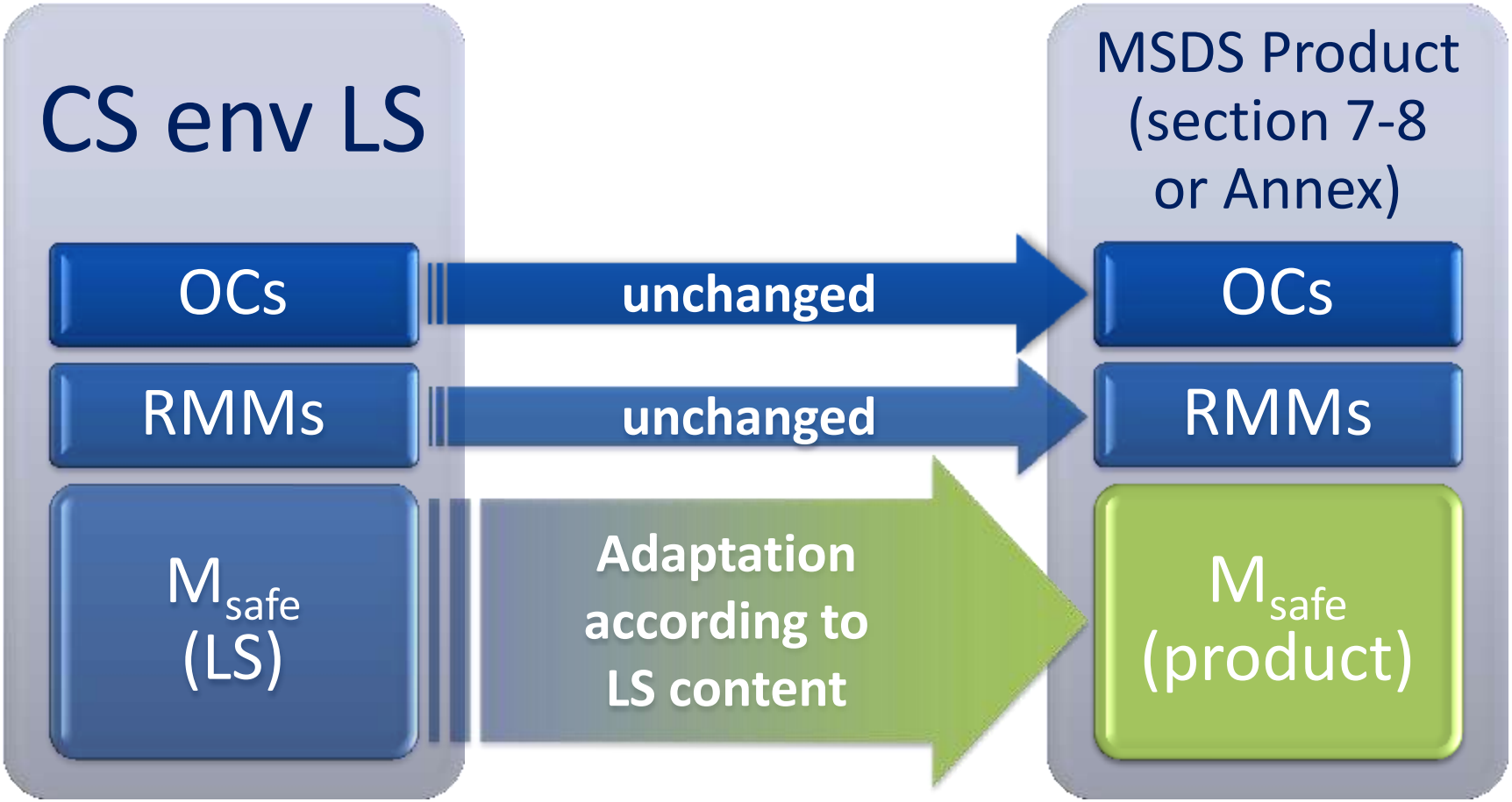
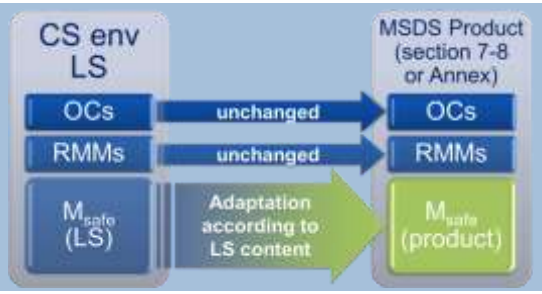
Contributing scenario environment of LS

- Operational conditions
- Risk management measures
- M_{safe}

Key role of M_{safe}



Example I



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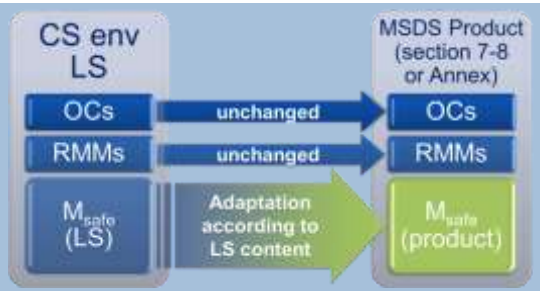
compound	[%]	Lead substance indicator	M_{safe}
water	80	none (no environmental classification)	n.a.
ABC	20	151	100 kg/d

M_{safe} LS / conc LS = M_{safe} product

100 kg/d → **100 / 0.2 = 500** → **500 kg/d**

Additivity



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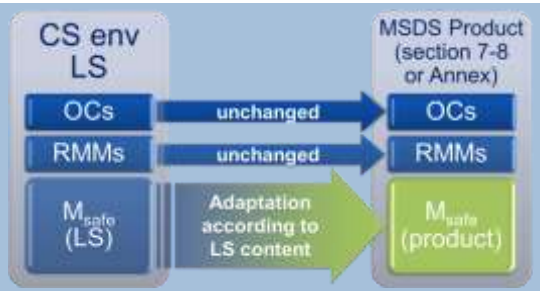
- If more than one compound of the mixture is classified for environmental hazards, potential additive effects may need to be covered.

- Therefore, the actual concentration of the Lead substance in the mixture may be converted – using a **modifying factor** – into a hypothetical concentration ("$\mathbf{C_{add}}$"), which also accounts for the additive(s).



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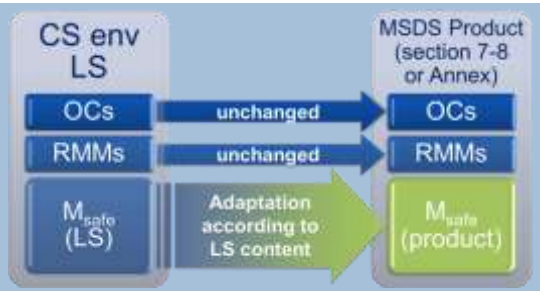
Modifying factor

$$MF = \frac{\Sigma\ LSI}{LSI\ max}$$

C_{add}

$$C_{add} = C_{LS} \times MF$$

Example II



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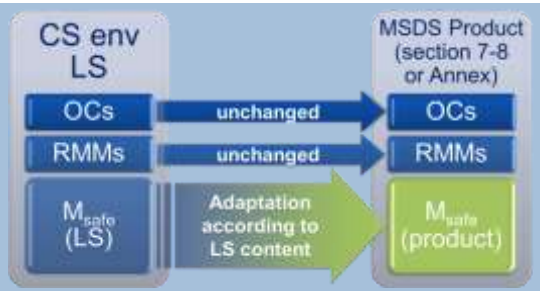
compound	[%]	Lead substance indicator	Msafe
water	65	none (no environmental classification)	n.a.
ABC	20	151	100 kg/d
DEF	10	none (no environmental classification)	n.a.
GHI	5	33	80 kg/d

$$MF = \frac{\Sigma \text{ LSI}}{\text{LSI max}} = \frac{151 + 33}{151} = \frac{184}{151} = 1.22$$

$$C_{add} = C_{LS} \times MF = 20 \times 1.22 = 24.4$$

Example II (continued)



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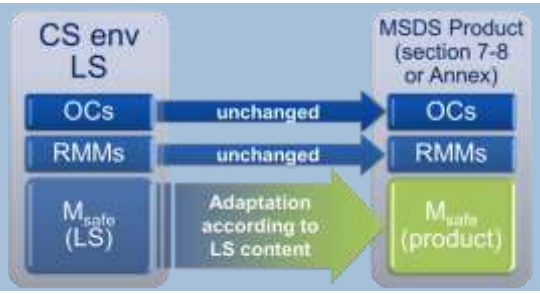
compound	[%]	Lead substance indicator	Msafe
water	65	none (no environmental classification)	n.a.
ABC	20	151	100 kg/d
DEF	10	none (no environmental classification)	n.a.
GHI	5	33	80 kg/d

$$M_{safe}\ LS\ /\ C_{add} = M_{safe}\ product$$

100 kg/d → **100 / 0.244 = 409** → **409 kg/d**

Final check



- The calculated M_{safe} for the product may be reviewed in the light of the intended application.
- In case of an unrealistic high value – e.g. because of a low LS content in the product – it may be an option to refine the OCs and RMMs of the scenario and adjust the M_{safe} accordingly.
- However, this procedure requires thorough judgment and expertise. Therefore, it should be carefully applied and well documented.

THANK YOU for your attention!