

# EU Regulatory needs – REACH and CLP

Workshop on Assessment of Respiratory  
Sensitization

28-29 May 2014, Alexandria, VA

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# REACH Regulation (EC) No 1907/2006

## ➤ **Registration**

- 2010, >1000 tonnes per year, CMR, vPvB
- 2013, > 100 tonnes per year
- 2018, > 1 tonne per year
- Non-phase in substances, continuously

## ➤ **Evaluation**

- Dossier Evaluation, ECHA
- Substance Evaluation, Member States

## ➤ **Authorisation**

## ➤ **Restriction**

## ➤ **ECHA also manages CLP Regulation 1278/2008**

## ➤ **For the purposes of this presentation, REACH is covered first**

# Evaluation



# Evaluation and Respiratory sensitisers - 1

## ➤ Dossier Evaluation

- Both tonnage driven hazard information (Annexes VII to X of REACH ) and Chemical Safety Assessment (Annex I) evaluated in a compliance check
- No legal standard information requirement of any test in Annexes VII to X for respiratory sensitisation
- Annex I defines chemical safety assessment and chemical safety report and covers sensitisation overall
- Guidance document Chapter R.7.a Endpoint specific guidance (paragraphs 7.3.5-7.3.9) describes how to use human and non-human data. As regards non-human data:
  - No definitive guidance on use of QSARs
  - No specific *in vitro* method
  - The role on LLNA, cytokine fingerprints, total IgE/specific IgE methods are described
  - Case-by-case assessment
- [http://echa.europa.eu/documents/10162/13632/information\\_requirements\\_r7a\\_en.pdf](http://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf)
- For sensitisers the chemical safety assessment can be based either on qualitative approach or quantitative risk characterisation (if quantitative Derived no-effect level (DNEL))

# Evaluation and Respiratory sensitisers -2

## ➤ Substance Evaluation

- Only substances listed in the Community Rolling Action Plan (CoRAP) are subject to substance evaluation
- “Further information” can be requested even beyond the information mentioned in Annexes VII to X of REACH, if there is a concern that a given substance may constitute a risk to human health or the environment, and further information is needed to clarify the concern
- Hazard or exposure information (up to 2014 only exposure information requested for respiratory sensitisers)
- For 13 out of 51 substances to be evaluated in 2014, the initial concern (or one of) is respiratory sensitisation
- The reason for concern and justifications are presented in the justification document prepared by the evaluating Member State and published (Community rolling action plan) :  
<http://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table>

# Authorisation and Restriction



# Main Risk Management Options for classified (CLP) Resp. Sensitisers under REACH

- **Authorisation** (REACH Title VII) *(Identification of the substance as SVHC and eventual inclusion in the 'List of Substances Subject to Authorisation' (REACH Annex XIV))*
  - ⇒ Authorisation covers all uses of an SVHC that are not generically or specifically exempted from authorisation. Purpose of authorisation is to progressively replace the SVHC by suitable alternative substances or technologies where these are economically and technically viable
  - ⇒ Prerequisite for subjecting a substance to the authorisation requirement is its identification as SVHC. Sensitisation is however no SVHC criterion of its own under REACH Art. 57. Therefore, a sensitising substance must be identified in accordance with Art. 57 (f) as giving rise to an equivalent level of concern to the cancerogenic, mutagenic or reprotoxic (CMR) substances covered by Art. 57 (a – c).
  
- **Restriction** (REACH Title VIII) *(If conclusion that there are unacceptable risks arising from uses of the substance)*
  - ⇒ Restrictions cover those uses for which unacceptable risks have been identified. The substance does not need to meet a specific hazard profile (e.g. SVHC). Purpose is control of risks (by banning those uses or by imposing conditions that render the risk acceptable). Other uses without unacceptable risks (if any) are not affected.
  
- **No action** *(If conclusion that no RRM beyond those already in place are required)*

## SVHC Identification of Sensitisers acc. Art. 57(f)

*Art. 57 (f): Substances [...] for which there is evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those other substances listed in points (a) to (e) and which are identified on a case by case basis [...]*

- Identification of a Sensitiser under 57(f) requires
  - Case by case justification
  - Comparison of the level of concern between CMRs and the Sensitiser

- General approach on identification as equivalent level of concern (ELoC) under article 57(f) agreed with MSs

[http://echa.europa.eu/documents/10162/19126370/dp\\_sensitisers\\_final\\_en.pdf](http://echa.europa.eu/documents/10162/19126370/dp_sensitisers_final_en.pdf)

Purpose of document:

- To support ELoC assessment for sensitisers in the context of the SVHC identification process under REACH

✓ **Factors which can be considered case by case**

X **Clear cut criteria providing a direct answer**



# SVHC Identification of Sensitisers acc. Art. 57(f)

## Level of Concern – Comparison factors

Comparison Factors	C & M	R	Resp. Sens.
<b>HEALTH EFFECTS</b>			
Possible serious health effects?	Yes	Yes	Yes
Irreversibility of health effects?	Yes	Yes	Induction: Yes Elicitation: Yes
Delay of health effects?	Yes	Yes	Yes
<b>OTHER FACTORS</b>			
<i>Quality of life impaired?</i>	Yes	Yes	Yes
<i>Societal concern?</i>	Yes	Yes	Yes
<i>Is derivation of 'safe concentration' possible?</i>	Normally No	Normally Yes	No

# SVHC Identification of Sensitisers acc. Art. 57(f)

## Level of Concern – Other Considerations

- Potency
  - Prevalence of cases plus severity of effects  $\approx$  indicator for potency
- Dose-response relationship
  - Difficult to identify quantitatively for sensitisers (similar to CMRs)
- Reactivity
  - Link between skin & resp. sensitisation
  - Elicitation can occur when exposed to similar substances

## **SVHC Identification of Sensitisers acc. Art. 57(f)**

- Generic considerations may apply to all classified Resp. Sensitisers
- Potential differentiating factors:
  - high frequency of occurrence in humans; or
  - a probability of a high sensitisation rate in humans based on animal or other tests
  - severity of reaction/effects may also be considered

## SVHC Identification of Sensitisers acc. Art. 57(f)

### Summary

- Identification of sensitisers as SVHCs based on Article 57(f) requires case by case:
  - Assessment of hazard properties and comparison of potential impact on health and other factors with that of CMRs and
  - Evidence that the substance is of equivalent level of concern (by concluding on results of comparison of hazard properties and potential impacts above). Consider all factors as one 'package'
  - Not all sensitisers fulfil the ELoC criterion
  - The current approach considers that the equivalent level of concern is more supported for respiratory sensitisers and sensitisers with serious and irreversible effects
  
- First 3 resp. Sensitisers identified as SVHCs (ELoC) and included in the Candidate List at the end of 2012

*(MHHPA , HHPA, Diazene-1,2-dicarboxamide)*

<http://echa.europa.eu/web/guest/candidate-list-table>

## Search for Sensitisers that potentially may require RRM

### ➤ **Roadmap for SVHC identification and implementation of REACH risk management measures from now to 2020**

<http://register.consilium.europa.eu/doc/srv?l=EN&t=PDF&gc=true&sc=false&f=ST%205867%202013%20INIT&r=http%3A%2F%2Fregister.consilium.europa.eu%2Fpd%2Fen%2F13%2Fst05%2Fst05867.en13.pdf>

- Defines a process, with clear deliverables, planning and share of responsibilities between the Commission, Member States and ECHA to achieve the 2020 Objective to have all relevant currently known SVHCs included in the Candidate List by 2020 (agreed spring 2013)

### Corresponding

### ➤ **Roadmap Implementation Plan (November 2013)**

[http://echa.europa.eu/documents/10162/19126370/svhc\\_roadmap\\_implementation\\_plan\\_en.pdf](http://echa.europa.eu/documents/10162/19126370/svhc_roadmap_implementation_plan_en.pdf)

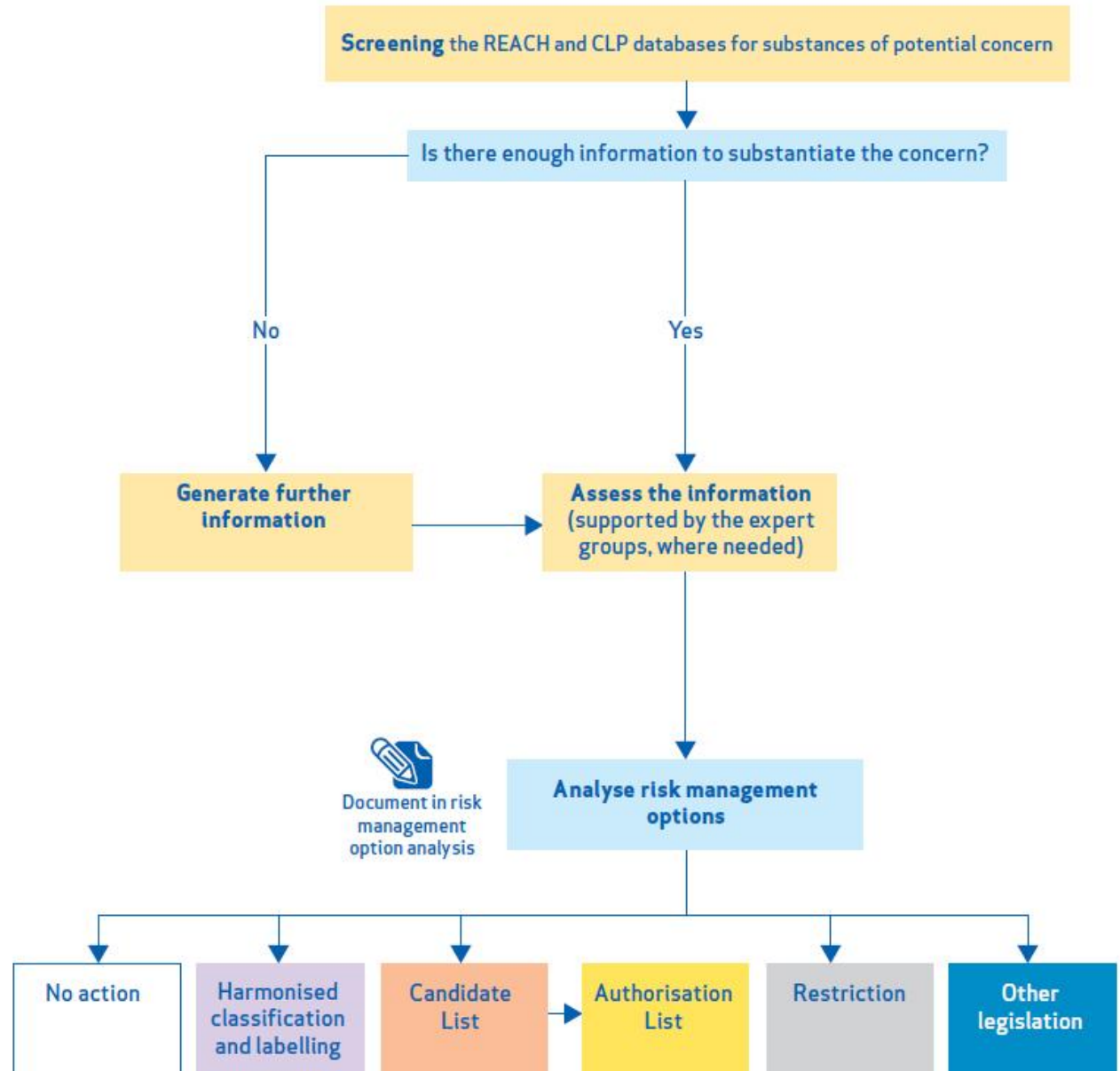
- Provides generic 'framework planning' on how main elements of the SVHC Roadmap to 2020 will be organised and linked to achieve the objectives of the SVHC Roadmap

# SVHC Roadmap to 2020 Implementation Plan

## Main elements with regard to SVHC identification

- Identification of 'Roadmap relevant' SVHCs
  - Screening for substances of concern (among them Sensitisers)
  - (Information generation and assessment)
  - Risk Management option (RMO) Analysis
  
- ⇒ Follow-up under relevant RRM processes

*Process flow to find substances in potential need of regulatory risk management measures (RRM)*



# CLP Regulation





## CLP Regulation 1272/2008 - Respiratory sensitisers

- **Respiratory sensitisers are among “substances of the highest concern” (Recital 52)**
- **Respiratory sensitiser means a substance that will lead to hypersensitivity of the airways following inhalation of the substance (Annex I section 3.4.1.1.)**

Category	Criteria
Category 1	<p>Substances shall be classified as respiratory sensitisers (Category 1) where data are not sufficient for sub-categorisation in accordance with the following criteria:</p> <p>(a) if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity; and /or</p> <p>(b) if there are positive results from an appropriate animal test.</p>
Sub-category 1A:	Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitisation rate in humans based on animal or other tests <sup>(1)</sup> . Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitisation rate in humans based on animal or other tests <sup>(1)</sup> . Severity of reaction may also be considered.
<p><sup>(1)</sup> At present, recognised and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.</p>	

## CLP Regulation 1272/2008, Annex I, Human data for respiratory sensitisers

- **Annex I: 3.4.2.1.2 Human evidence**
- **Annex I: 3.4.2.1.2.1.** Evidence that a substance can lead to specific hypersensitivity will **normally** be based on human experience. In this context, hypersensitivity is **normally** seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. **However, immunological mechanisms do not have to be demonstrated.**
- ...
- **Annex I: 3.4.2.1.2.3.** The evidence referred to above could be:
  - (a) clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include:
    - (i) in vivo immunological test (e.g. skin prick test)
    - (ii) in vitro immunological test (e.g. serological analysis);
    - (iii) studies that indicate other specific hypersensitivity reactions where immunological mechanisms of action have not been proven, e.g. repeated low-level irritation, pharmacologically mediated effects;
    - (iv) a chemical structure related to substances known to cause respiratory hypersensitivity;
  - (b) data from one or more positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

## CLP Regulation 1272/2008, Annex I, Non-human data for respiratory sensitisers

### 3.4.2.1.3.2 Non human data on respiratory sensitisation

#### Annex I: 3.4.2.1.3. Animal studies

**Annex I: 3.4.2.1.3.1.** Data from appropriate animal studies (\*) which may be indicative of the potential of a substance to cause sensitisation by inhalation in humans (\*\*) may include:

- (a) measurements of Immunoglobulin E (IgE) and other specific immunological parameters in mice;
- (b) specific pulmonary responses in guinea pigs.

(\*) At present, recognised and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.

(\*\*) The mechanisms by which substances induce symptoms of asthma are not yet fully known. For preventative measures, these substances are considered respiratory sensitisers. However, if on the basis of the evidence, it can be demonstrated that these substances induce symptoms of asthma by irritation only in people with bronchial hyper reactivity, they should not be considered respiratory sensitisers.

## Guidance on application of the CLP Criteria, paragraphs 3.4.2.1.3.2. and 3.4.2.1.5.

- No formally recognised and validated animal tests currently exist for respiratory sensitisation. However data from some animal studies may be indicative of the potential of a substance to cause respiratory sensitisation in humans (CLP Annex I, 3.4.2.1.3) and may provide supportive evidence in case human evidence is available (see also section 3.4.2.1.2 above). This information may also be combined with information on structural alerts for respiratory sensitisation (see the Guidance on IR/CSA, Section R.7.3.5.1) and information on the skin sensitising properties of a substance and should be **used in a weight of evidence assessment** (see the Guidance on IR/CSA, Section R.7.3.6.1).
- Information on sensitizing activity of substances, such as that identified using contact sensitivity studies, can also be taken into consideration and **used in a weight of evidence assessment**, because there may be a relationship between the skin sensitising properties of a substance and the respiratory sensitising properties. The interpretation is therefore that a substance which fails to induce a positive response in the LLNA (at an appropriate test concentration and with the exception of large substances such as enzymes) most probably lacks the potential for respiratory allergy. Conversely, it cannot be excluded that a chemical that induces a positive response in the LLNA, might sensitise the respiratory tract upon inhalation or via dermal exposure.
- **Respiratory sensitisers cannot be identified reliably on the basis of animal tests as yet**, since no recognised validated test exists to determine sensitising **potential** and **potency** by inhalation. Therefore specific concentration limits (SCLs) cannot be set on the basis of animal data alone. Moreover, there is no concept available to set SCLs on the basis of human data for respiratory sensitisers.
- [http://echa.europa.eu/documents/10162/13562/clp\\_en.pdf](http://echa.europa.eu/documents/10162/13562/clp_en.pdf)

# Conclusions



## Conclusions

- In the absence of a validated standard method, case-by-case judgement and weight-of-evidence approaches necessary for regulatory purposes (hazard information and classification). Not an optimal situation for a health effect as important as respiratory sensitization.
- For SVHC identification, respiratory sensitizers are covered under “ELoC” concept of the Article 57(f) of REACH.
- For both REACH processes and CLP, there is a need to differentiate between respiratory sensitizers according to their sensitizing potential and potency.
- In a regulatory framework, an information request (test data or tiered approaches) would need to be such, that a reasonably definitive answer to the concern is delivered.
- Challenges for (test) data
  - Induction vs. elicitation (vs. both)
  - Route of exposure
  - Potency, Dose-response

Thank you!

