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Overview of human non-dietary exposure prediction and respective tools in different regulations.

25 March 2025, GT Advanced Course, 10th German Pharm-Tox summit, Hannover
Dr Sven Ruhl

Regulatory solutions for your key market



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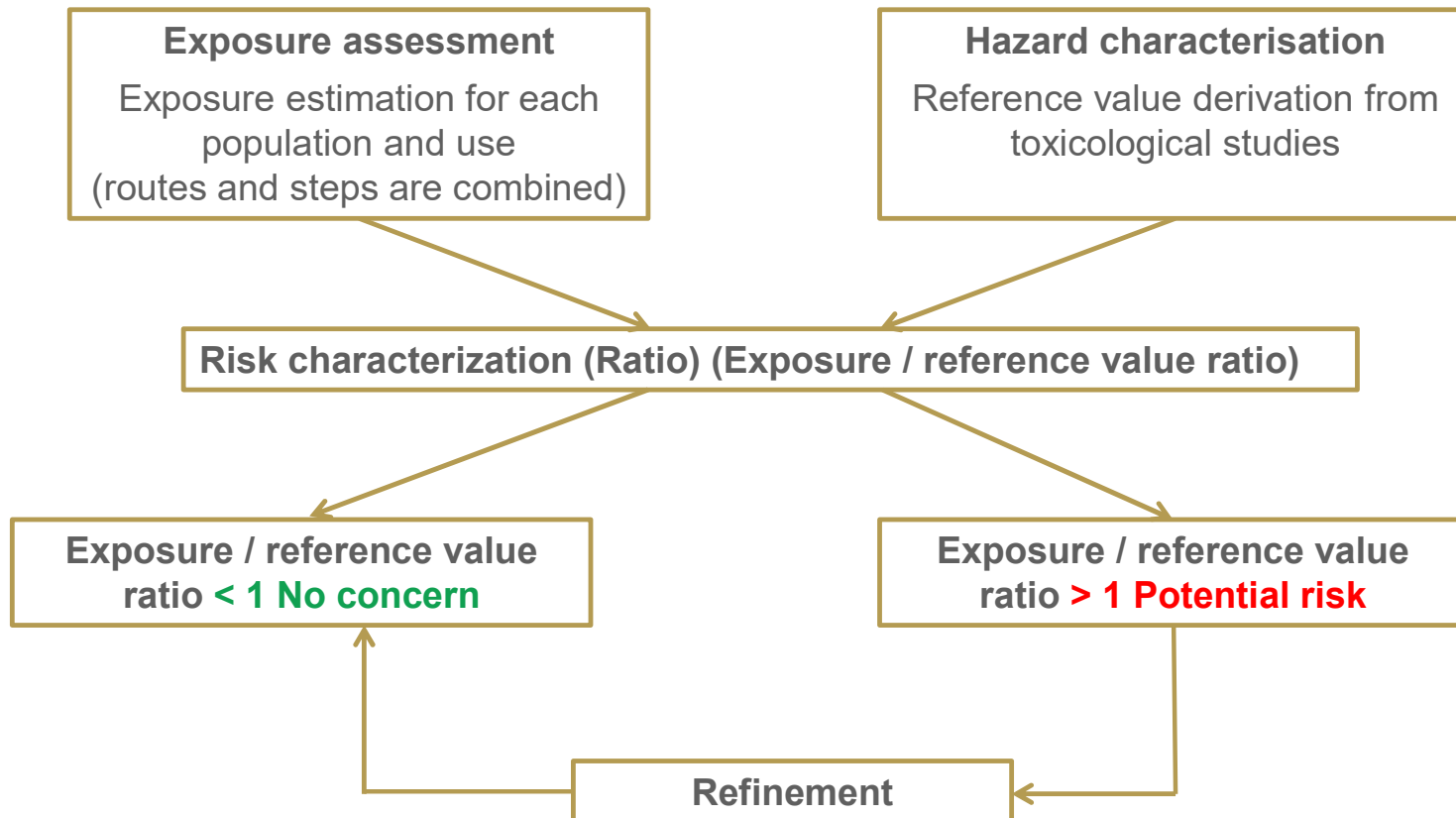
MEDICAL DEVICES

- ▶ Overview of human non-dietary exposure prediction
- ▶ Exposure prediction tools in different regulations:
 - ▶ Chemicals: REACH Regulation (EC) No 1907/2006
 - ▶ Plant Protection Products: Regulation (EC) No 1107/2009
 - ▶ Biocidal Products: Regulation (EU) No 528/2012
- ▶ Cross-talks
- ▶ Upcoming developments
- ▶ Wrap-up



Overview of human non-dietary exposure prediction





Overview of human non-dietary exposure prediction

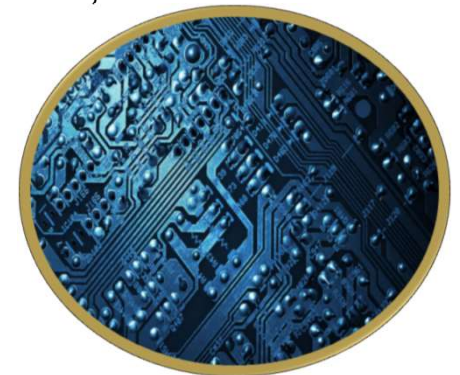
- ▶ For risk characterization quantification of potential exposure is required;
- ▶ Information on exposure is not always available;
- ▶ Exposure models developed (qualitative / theoretical and quantitative / numerical);
- ▶ Exposure models can be defined as a mathematical representation of exposure processes;
- ▶ Essential input parameters are required to estimate exposure quantitatively.



Overview of human non-dietary exposure prediction

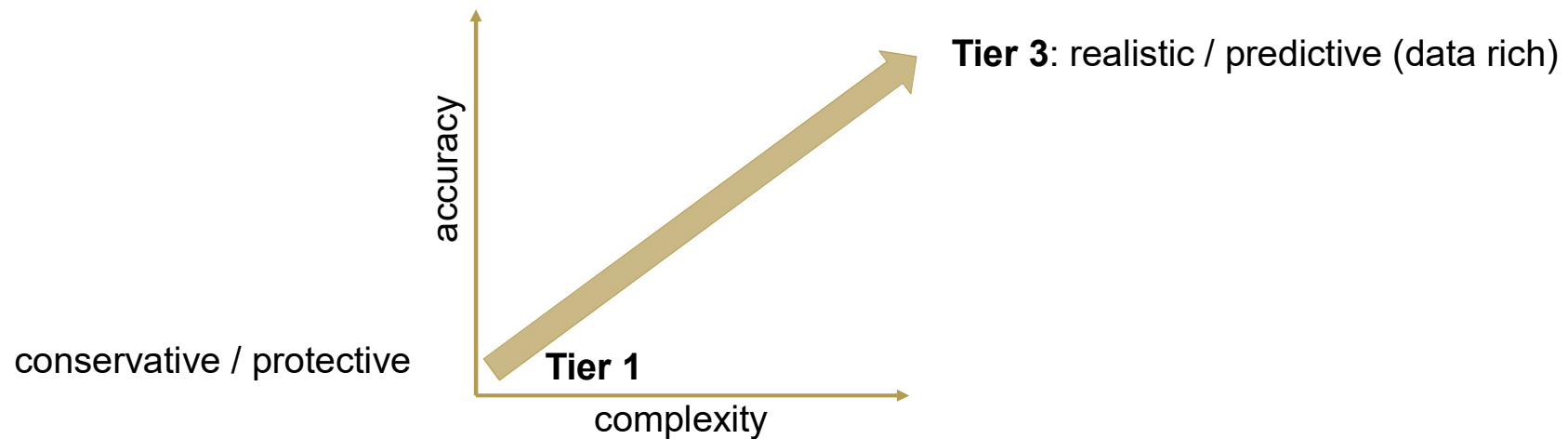
- ▶ Exposure may be modelled by building a scenario and applying known physical, chemical, or biological laws.
 - Normally fixed input parameters with single output value based on defined algorithm;
 - “relatively simple”.

- ▶ Exposure may be modelled by using measured data and statistical analysis.
 - Rely on patterns observed in data;
 - Can be very specific for the measured exposure situation;
 - Variability in input parameter can be considered to provide probability distributions (confidence intervals).



Overview of human non-dietary exposure prediction

- Exposure modelling “typically” a tiered approach:



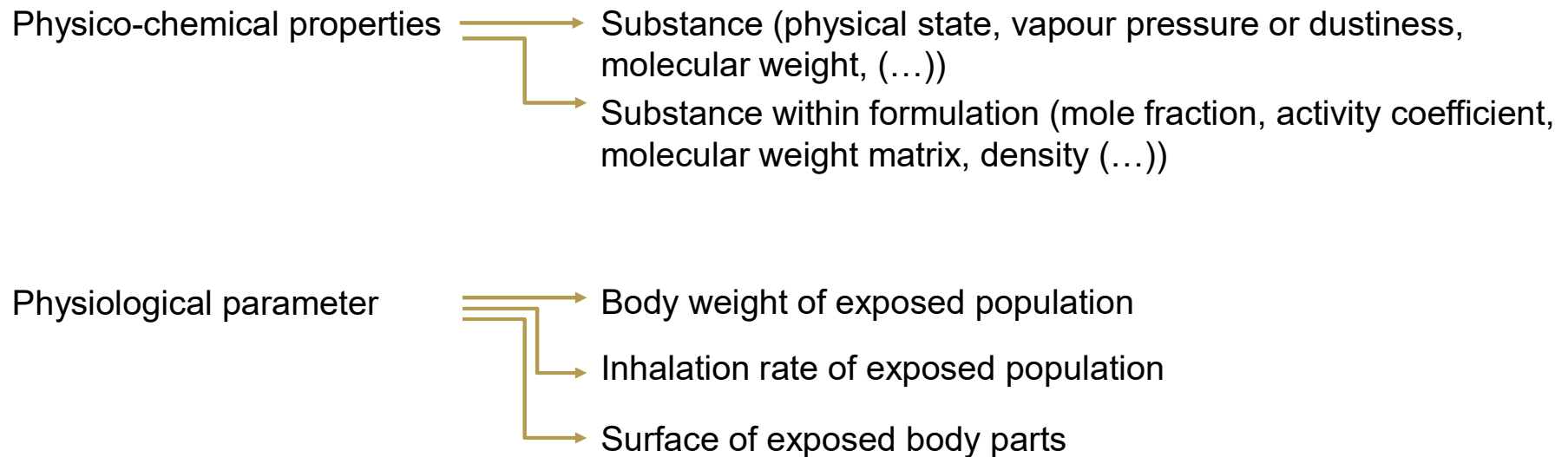
- Tier 1 exposure models consider worst case assumptions based on input parameters
 - often refinements to show an acceptable exposure

Overview of human non-dietary exposure prediction

- ▶ Higher tier refinements become more realistic by
 - More accurately modelling exposure (e.g. better description of vapour-liquid equilibria for multi-component mixtures).
 - Using more specific indicative exposure values for the relevant exposure scenario / use.
 - Combining indicative values from several exposure data for a certain exposure scenario and providing confidence intervals.
 - Allowing combination of indicative values with measured data to improve confidence.

Overview of human non-dietary exposure prediction

► Essential input parameters



Overview of human non-dietary exposure prediction

► Essential input parameters

Use related parameters

- Concentration of substance
- Duration of exposure
- Amount used
- Frequency of exposure
- Place of use
- Room volume
- Ventilation rate
- Local exhaust ventilation
- Respiratory protection
- Dermal protection (gloves / coverall)
- Transfer coefficients

Overview of human non-dietary exposure prediction

- ▶ „Already easy and simple Tier 1 approach“ → knowledge of a number of input parameters required;
- ▶ Defaults available for physiological parameters e.g.
 - respiratory volume at different activity levels and ages;
 - body weights
 - (...).
- ▶ Defaults available for typical uses / activities e.g.
 - amount used;
 - duration of exposure;
 - (...) as well
- ▶ Defaults are
 - built-in into the exposure model
 - might need to be derived from guidance's and considered manually



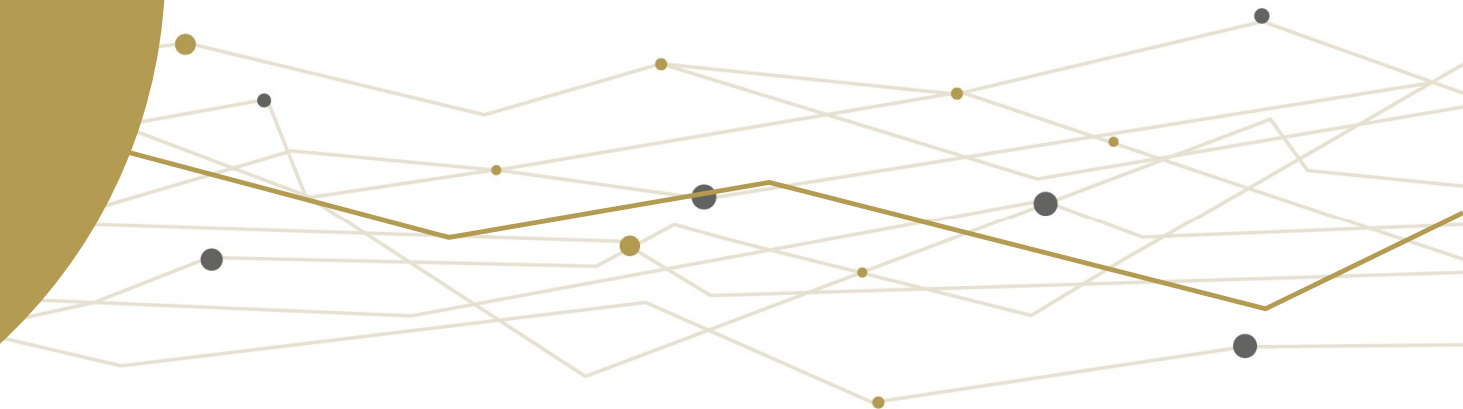
Exposure prediction tools in different regulations





Chemicals

Chemicals - REACH Regulation



How to describe a **Use** under REACH?

| Use Descriptor Category | Related key element | Example |
|--------------------------------------|---|---|
| Life cycle stage (LCS) | Life cycle stage | <i>Industrial Use</i> |
| Sector of use (SU) | Market description (sector of economy where the use takes place) | <i>SU 6b, Manufacture of pulp, paper and paper products</i> |
| Process category (PROC) | Contributing activities (workers) | <i>PROC 5, Mixing or blending in batch processes</i> |
| Environmental release category (ERC) | Contributing activities (environment) | <i>ERC 5, Use at industrial site leading to inclusion into/onto article</i> |
| Article category (AC) | Market description (type of article), Contributing activities (service life) | <i>AC 8b, Paper articles</i> |
| Product category (PC) | Market description (type of product), Contributing activities (consumers) | <i>PC 26, Paper and board treatment products</i> |
| Technical function (TF) | Technical function of the substance | <i>Processing aid</i> |

Where?
How?
What?
Why?

“Specific considerations regarding tools” - Chemicals

- ▶ REACH related exposure modelling quite exhaustive. Especially the Tier 1 tool must be:
 - Reliably conservative

- ▶ But in parallel the tool ideally
 - Is easy to use
 - Is user friendly
 - Has logics avoiding mistakes (e.g. submitting unacceptable risks)
 - Allows exposure assessments in “batches”
 - Allow inclusion (and reporting) of higher tier modelling
 - Supports standardised outputs
 - Allows data exchange with standard information database of ECHA

Overview of accepted tools - Chemicals

- Summary of the major human health exposure assessment tools that are widely accepted for CSA under REACH

| Tool | Tier | Route of exposure | Process / Task | Physical state |
|----------------------------------|--------|--|----------------|--|
| ECETOC TRA | Tier 1 | Inhalation Dermal (oral for consumers) | Process based | solids and liquids |
| CHESAR | Tier 1 | Inhalation Dermal (oral for consumers) | Process based | solids and liquids |
| EMKG – Expo Tool | Tier 1 | Inhalation | Task based | solids and liquids |
| MEASE | Tier 1 | Inhalation Dermal | Process based | solids, liquids and gases For metals and inorganic substances |
| Stoffenmanager | Tier 2 | Inhalation | Task based | solids and liquids |
| RiskofDerm | Tier 2 | Dermal | Task based | solids and liquids |
| Advanced REACH Tool (ART) | Tier 2 | Inhalation | Task based | solids and liquids |
| ConsExpo | Tier 2 | Inhalation Dermal Oral | Task based | solids and liquids |

CSA: Chemical Safety Assessment

Exposure prediction tools – Chemicals – ECETOC TRA tool



- Tier 1 Exposure tool needs to be sufficiently conservative and allow high throughput (for relevant routes of exposure)

| Human Health Assessment - Workers | | | | | | |
|-----------------------------------|---------------|-------------------------|---|---|---|--|
| No. | Scenario name | Process Category (PROC) | Type of setting (PROC 7 and 22 always industrial, PROC 11 and 20 <i>not applicable</i>) | Is substance a solid? (yes/no) | Dustiness of solids OR VP of volatiles (Pa) at process temperature (clear entries if you change column F to "No") | Duration of activity (hours/day) |
| Human Health Assessment - Workers | | | | | | |
| No. | Scenario name | Process Category (PROC) | Use of ventilation? (addresses outdoor use, LEV and general ventilation) Note: LEV in combination with enhanced general ventilation for industrial only! | Use of respiratory protection and, if so, minimum efficiency? | Substance in preparation? (applies to inhalation and dermal for volatiles and solids) | Consider LEV for dermal exposure? (conservative default is "No" if entry left blank) |
| 1 | example 1 | PROC 8a | Outdoors | No | No | Yes |
| 2 | | PROC 1 | Indoors | 90% | < 1% | No |
| 3 | | PROC 2 | Indoors with LEV | 95% | 1-5% | |
| 4 | | PROC 3 | Indoors with good general ventilation | | 5-25% | |
| 5 | | PROC 4 | Indoors with enhanced general ventilation | | > 25% | |
| 6 | | PROC 5 | Indoors with LEV and good general ventilation | | | |
| 7 | | PROC 6 | | | | |
| 8 | | PROC 7 | | | | |
| 9 | | PROC 8a | | | | |
| 10 | | PROC 8b | | | | |
| 11 | | PROC 9 | | | | |
| 12 | | PROC 10 | | | | |
| 13 | | PROC 11 | | | | |
| 14 | | | | | | |
| 15 | | | | | | |

for debugging scenario no. 1



- ▶ Tier 1 Exposure tool needs to be sufficiently conservative and allow high throughput (for relevant routes of exposure)

| Duration of activity | Exposure modifying factor |
|----------------------|---------------------------|
| > 4 hours (default) | 1 |
| 1 - 4 hours | 0.6 |
| 15 min - 1 hour | 0.2 |
| < 15 min | 0.1 |

| Concentration in mixture (w/w) | Exposure modifying factor |
|--------------------------------|---------------------------|
| Not in a mixture | 1.0 |
| >25% | 1.0 |
| 5-25% | 0.6 |
| 1-5% | 0.2 |
| <1% | 0.1 |

For aerosols air concentrations are calculated considering „instantaneous release“

Uses and exposure scenarios – Chemicals

- Some trade associations develop **use maps** to support industry covering relevant uses

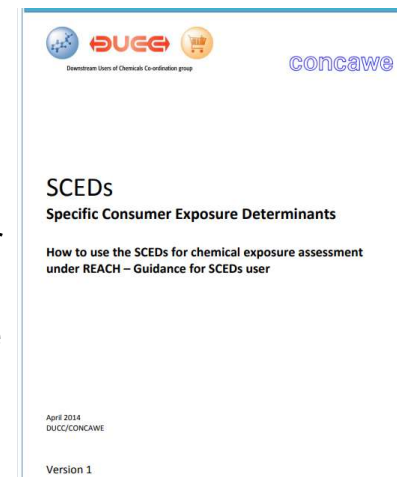
v EFCC
European Federation for Construction Chemicals

| | | | | | | | | | | |
|--|--|----------------------------|---------------------------------------|---------------------------------|---------------------------|-------------------------------|--|---------------------|--|---|
| v A: Inte Se Se Se | <div style="background-color: #e0e0e0; padding: 5px; margin-bottom: 5px;"> v CLE CropLife Europe </div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 35%; padding: 5px;">Sector acronym/name</td> <td style="padding: 5px;">CLE / CropLife Europe</td> </tr> <tr> <td style="padding: 5px;">Sector products coverage</td> <td style="padding: 5px;">Plant protection products</td> </tr> <tr> <td style="padding: 5px;">Sector substance types</td> <td style="padding: 5px;">Liquid and solid substances used as co-formulants in plant protection products</td> </tr> <tr> <td style="padding: 5px;">Covered uses</td> <td style="padding: 5px;">Professional use and consumer use of plant protection products (spray application, granular application including treated seeds)</td> </tr> </table> | Sector acronym/name | CLE / CropLife Europe | Sector products coverage | Plant protection products | Sector substance types | Liquid and solid substances used as co-formulants in plant protection products | Covered uses | Professional use and consumer use of plant protection products (spray application, granular application including treated seeds) | Chemicals inorganic pigments, sional use of s of substances - e.g. solvents, additives, fillers, |
| Sector acronym/name | CLE / CropLife Europe | | | | | | | | | |
| Sector products coverage | Plant protection products | | | | | | | | | |
| Sector substance types | Liquid and solid substances used as co-formulants in plant protection products | | | | | | | | | |
| Covered uses | Professional use and consumer use of plant protection products (spray application, granular application including treated seeds) | | | | | | | | | |

| | | |
|---------------------|---|---|
| Covered uses | Typical industrial, professional and consumer (end)uses of detergent products | Industrial uses, Professional uses, Consumer uses |
| Covered uses | Formulation, professional use and consumer use of cosmetic products. | de variety of substances, e.g. plant preservatives, surfactants, etc. |

Uses and exposure scenarios – Chemicals

- ▶ Sector-specific **worker** exposure descriptions (**SWEDs**) additionally inform on operational conditions and RMMs.
 - Conditions of use not only for ECETOC TRAv3 but Advanced REACH Tool v1.5, MEASE 2, Stoffenmanager v8 and EMKG-Expo tool v2.0
- ▶ Specific **consumer** exposure determinants (**SCEDs**) inform on conditions of use for substances in consumer products.
 - This includes information on the design of a consumer product type (e.g. package size and design) and information on the habits and practices of how consumers actually use the products



Exposure prediction tools – Chemicals - CHESAR



- ▶ Based on ECETOC TRAv3 ECHA developed the **CHE**mical **S**afety **A**ssessment and **R**eporting tool (CHESAR)
 - to ease reporting and standardise workflow as well as reporting / communication in supply chain;
- ▶ Like ECETOC TRAv3 it is applicable for solids and liquids;
- ▶ Gases, emission from hot processes, solids in liquids or fibres are out of applicability domain;
- ▶ Allows implementation of external tools (Advanced REACH Tool, RiskofDerm...).



- ▶ **Advanced REACH Tool (ART)** is activity based BUT allows building scenarios with up to four activities.
- ▶ Like ECETOC TRAv3 it is applicable for solids and liquids.
- ▶ Gases, emission from hot processes, fibres are out of applicability domain.
- ▶ Allows detailed assessment of activities.



Exposure prediction tools – Chemicals - ART

- ART input options; Example “PROC 8a: Transfer at non-dedicated filling lines”

| Inputs | option | | | |
|-------------------------------------|---|--|-------------|--------------------------|
| Activity | Transfer of substance | | | |
| Activity subclass | - Bottom loading | - Falling liquid | | |
| Flow rate of transfer | <0.1 (L/min) | till >1000 | | |
| Containment | - Open process | - Reduced contact to air | | |
| Loading type | - Splash loading | - Submerged loading | | |
| Primary localised controls | - Containment* | - LEV* | - Glove box | - Vapour recovery system |
| Secondary localised controls | - Containment* | - LEV* | - Glove box | - Vapour recovery system |
| Containment | - Yes | - No | | |
| Site | Indoor* | Outdoor* | Spray room* | Downward laminar flow* |
| Size of work room m3 | Any - Large - Small | 30 / 100 / 300 / 1000 / 3000 (m3) | | |
| Ventilation | - No - Good natural - Mechanical - Specialised | 0.3 / 1 / 3 / 10 / 30 (air change per hour) | | |
| Secondary emission sources | Yes | No | | |

* Including kind or level of control





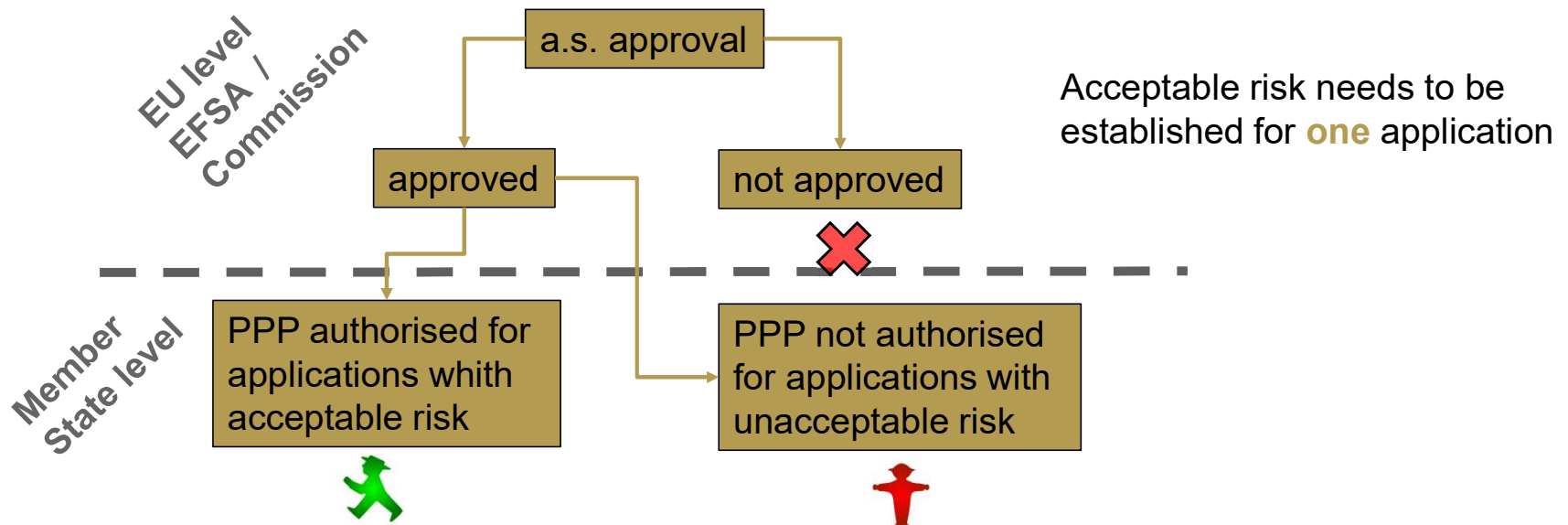
Crop protection

Plant Protection Product Regulation



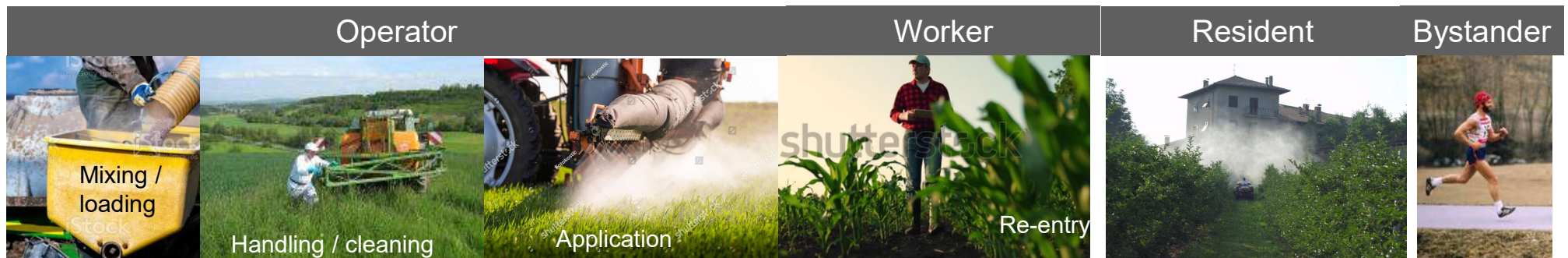
The two step procedure under PPPR

- Approval of active substances at EU level
- Authorisation of biocidal products in Member States



Exposure prediction tools – Plant protection

- ▶ The exposure assessment of PPP has to address all tasks / activities and related exposures of the substance
- ▶ “different input” parameters (e.g. kg/ha)
- ▶ “different activities and target populations” – different underlying exposure data



EFSA guidance on the assessment of exposure in combination with online calculator (2022)

► Major updates (compared to 2014)

- Inclusion / update of data for uses for different applications
- Incorporation of additional scenarios, e.g. dustable powder formulations
- Update of the default values used in the Guidance (and calculator)
- Update of the scenarios considering new information as regards personal protective equipment (PPE) and technical equipment or packaging

Updated calculator published 2025

WELCOME TO OPEX

This tool is developed to provide estimates of the non-dietary exposure (for operators, workers, residents and bystanders) related to the use of plant protection products, therefore allowing a conclusion on the non-dietary risk assessment for these products. It has been developed based on the following EFSA Guidance documents:

- ▶ **Correction of Calculated Values:** Ensures accuracy in exposure estimates.
- ▶ **Increased Flexibility:** Allows for more varied and realistic scenarios.
- ▶ **Generation of Different Reports:** Provides tailored outputs for different stakeholders.

Number 1 exposure tool – for low- and semi-volatile active substances for standard exposure assessments

“Experience regarding refinements” – Plant protection

- ▶ Standard uses must be modelled using OPEX-tool.

- ▶ Acceptance of refinements by other tools may be limited.

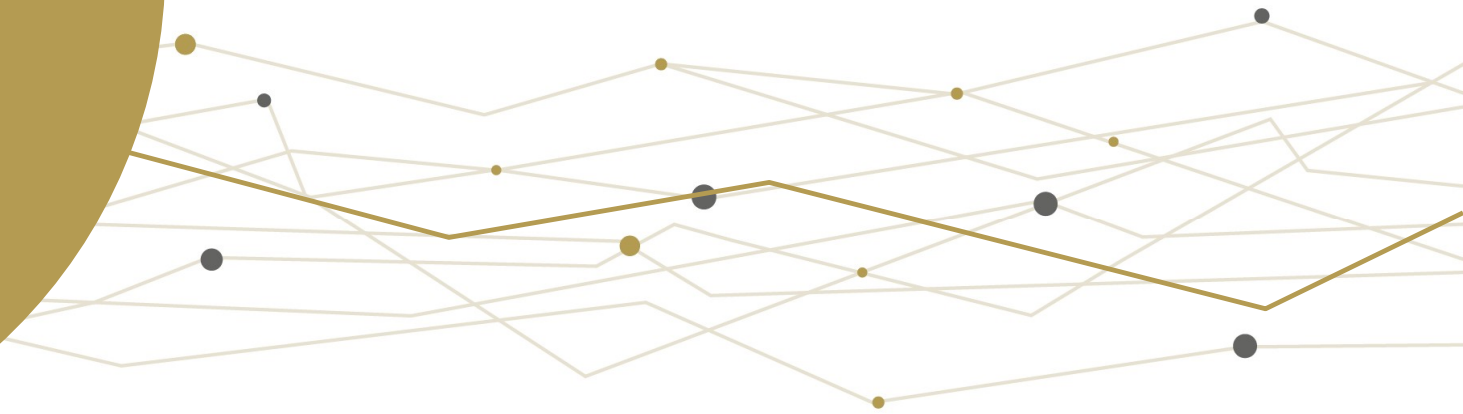
- ▶ Acceptance of studies for refinements:
 - Dislodgeable Foliar Residue (DFR) acceptable
 - Operator exposure (OpEx) studies may be limited

- ▶ Non-standard uses (painting trees, dipping of fruits, “drawing”) can be assessed with models outside PPP.



Biocides

BPR – Biocidal Product Regulation



Exposure assessment – human health – Biocidal products

- Based on their intended use and type of organisms to be controlled, biocidal products (b.p.) are categorised into 22 Products Types (PT).

Group 1 Disinfectants PTs 1 - 5



Group 2 Preservatives PTs 6 - 13



Group 3 Pest control PTs 14 - 20



Group 4 Other b.p. PTs 21 - 22



- Information source for human health exposure assessment models that are widely accepted for BPR

Ad hoc Working Group - Human Exposure

The Ad hoc Working Group on Human Exposure will support the Biocidal Products Committee and its Working Groups (especially the Working Group on Human Health) with issues related to human exposure to biocides, including among others:

- Technical or scientific matters as well as generic or specific methodological issues
- Harmonisation of the approach for assessing human exposure to biocides
- Implementation of the strategies of biocides exposure assessment
- Identification of the needs to revise the existing guidance documents on human exposure to biocidal products and contribution to the revision, where appropriate

Chair of the Working Group: Carmen Estevan Martinez

No specific tier I exposure tool available – individual assessments based on use description

RELATED

- [Opinions of the Human Exposure Expert Group \(HEEG\)](#)
- [Recommendations of the Ad hoc Working Group on Human Exposure](#)
- [Biocides Human Health Exposure Methodology \(117MB\) \[RTF\]](#)
- [BPR Guidance Volume III Human health Part B](#)

Exposure Assessment Recommendations – Biocidal products

- ▶ Clear use description necessary to identify correct exposure model
- ▶ Photos and videos are very effective to visualize the scenario to the assessor
- ▶ ConsExpo a common tool to assess exposure



←
Back

Outdated exposure data leading to overestimation of biocides risks - RIVM

CHEMICAL WATCH NEWS

28 January 2025

Dutch institute calls for large-scale assessment of old studies

Models may not cover „new“ application methods

“Specific considerations regarding tools” – Biocidal products



- ▶ Using default parameters from the Recommendations are typically accepted.
- ▶ Models and input parameters need to be chosen very carefully.
- ▶ Deviating from Recommendations needs to be well justified.
- ▶ Considering “product specific” refinements can be considered and accepted (e.g. spray pattern from trigger sprayer, release rate by spray trigger).
- ▶ Operator exposure data may more reasonably be accepted. At least can be used to define relevant indicative values.

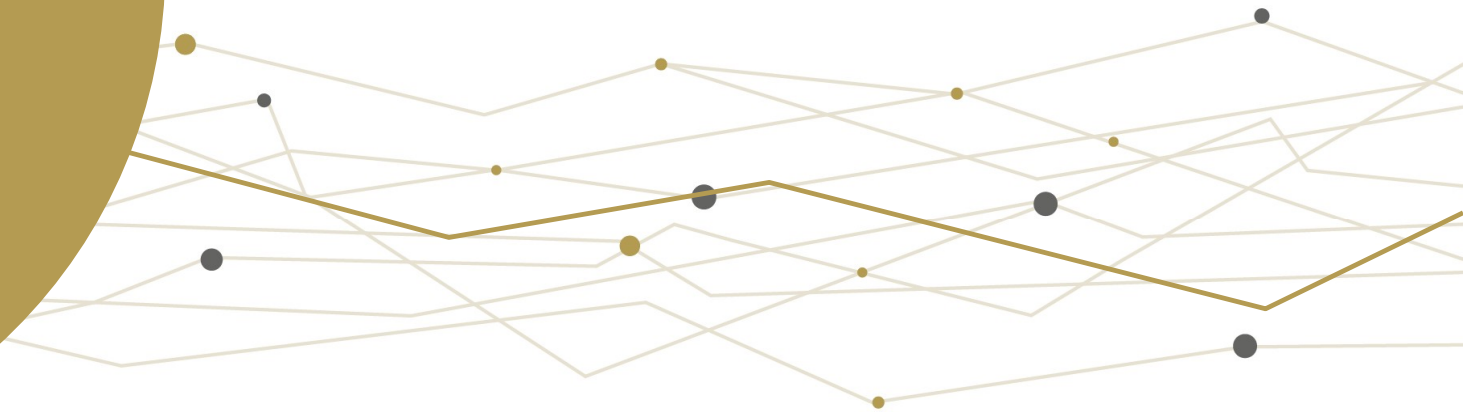


Chemicals



Crop protection

Existing cross talks



Existing cross-talks – human health exposure assessments

- ▶ Active substances are (normally) not subject to REACH
- ▶ Co-formulants however are subject to REACH under certain circumstances

“Translation” of identified uses into use descriptor system of ECHA

- ▶ Some trade associations develop use maps to support

| ▼ CLE CropLife Europe | |
|--------------------------|--|
| Sector acronym/name | CLE / CropLife Europe |
| Sector products coverage | Plant protection products |
| Sector substance types | Liquid and solid substances used as co-formulants in plant protection products |
| Covered uses | Professional use and consumer use of plant protection products (spray application, granular application including treated seeds) |

Existing cross-talks – human health exposure assessments

CropLife Europe - Operator Worker Bystander Tool (CLE - OWB)

CLE OWB v4.1

extera
Expertise In Toxicology, Exposure and Risk Assessment



| | | | | | |
|---|-------------------------------|--------------------------|--|-----------------------|-------------------------------|
| Substance | | | | | |
| Substance data | | | | | |
| Vapour pressure (room temp.) | 1,00E+00 | | Pa | | |
| Physical state (room temp.) | liquid | | | | |
| DNELs | | | | Comments | |
| Worker, long term, inhalation | 1,00 | mg/m ³ | | | |
| Worker, long term, dermal | 1,00 | mg/kg bw/day | | | |
| General population, long term, inhalation | 1,00 | mg/m ³ | | | |
| General population, long term, dermal | 1,00 | mg/kg bw/day | | | |
| Scenario information | | Professional uses | | Consumer uses | |
| ES no. | PPP GES1 Spray application | | PPP GES2 Seed and granular application | PPP GES3 | PPP GES4 |
| ES sub-activity | Tractor-mounted spraying | Hand-held spraying | Dispersing granules/ seeds | Hand-held spraying | Dispersing granules/ seeds |
| Application rate (kg/ha) | 1,00 | 1,00 | 20,0 | 1,00 | 1,00 |
| Personal protection (PPE) | Gloves M&L | Gloves M&L | Work wear + gloves | | |
| Respiratory protection (RPE) | no RPE | no RPE | no RPE | | |

Maximum rate

Report PPP GES

Create CSR

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Existing cross-talks – human health exposure assessments

- ▶ Agricultural input parameters can be used
- ▶ Default efficiency of RMMs
- ▶ Combines relevant activities and provides RCRs for combined exposures
- ▶ Reporting ready to use for CSA Report

Table 9.13: Exposure estimates and RCRs for combined Worker CS

| Contributing Scenarios | Use rate | | Dermal exposure [mg/kg bw/day] | Inhalation Exposure [mg/m ³] | Dermal RCR | Inhalation RCR | Total RCR |
|--|----------|--------|--------------------------------------|---|-------------|----------------|-------------|
| | [kg/ha] | [kg/d] | | | | | |
| Tractor-mounted boom spraying | | | | | | | |
| PROC 8a: Mixing & loading liquid formulation | 1,00 | 50,00 | 0,01 | 0,001 | 0,01 | 0,01 | 0,02 |
| PROC 11: Tractor-mounted boom spraying | | | 0,11 | 0,001 | 0,11 | 0,01 | 0,12 |
| PROC 8a+11 | | | 0,12 | 0,002 | 0,12 | 0,002 | 0,14 |

Helpful tool to support exposure assessments for chemicals used in plant protection products



Chemicals

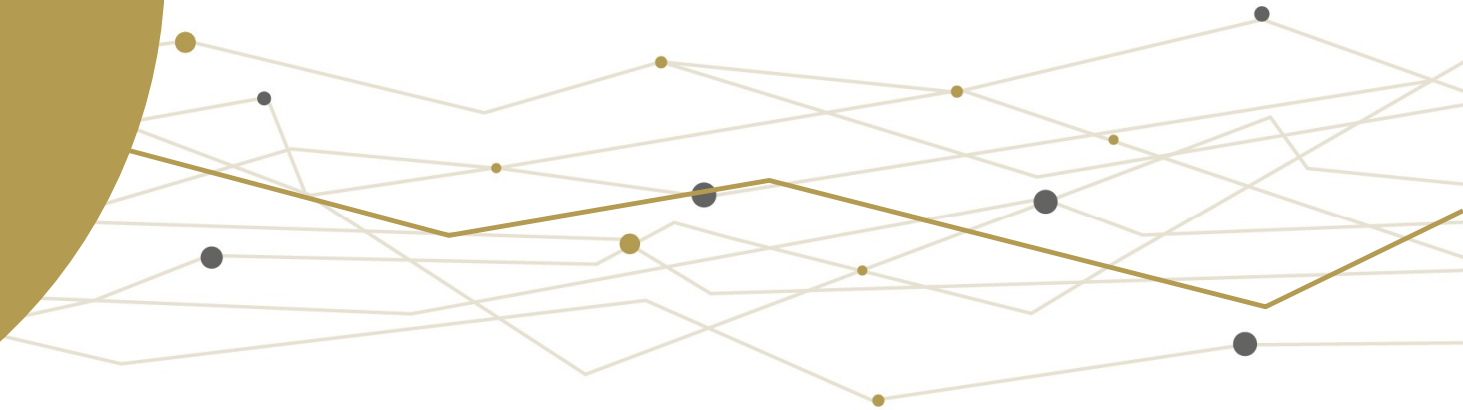


Biocides



Crop protection

Upcoming developments



Upcoming developments – human health exposure tools

Biocide Stakeholders' Workshop

Helsinki/online | 29/04/2025 - 30/04/2025 | 09:00 - 13:30

Times are in EET, GMT +2

Add to calendar

| SESSION 2 IT TOOLS FOR BPR: FUTURE DEVELOPMENTS | |
|--|--|
| 12:00–12:15 | Plans for R4BP 3 evolution ECHA |
| 12:15–12:30 | IUCLID development to achieve good quality data ECHA |
| 12:30–12:45 | Chesar platform for biocides: updates on the project ECHA |

Day 2

- IUCLID for biocides
- Submissions of IUCLID files for summaries of product characteristics
- Demo on the Chesar platform for chemical safety assessment and reporting.



Crop protection



Upcoming developments – human health exposure tools



Mixture Assessment Factor?



Closed consultation

An alternative transitional registration model (ATRm) for UK REACH

Detail of feedback received

Thank you to everyone who responded to this consultation. We received 241 responses from a wide range of stakeholders and interested parties.

We are currently considering our approach to chemicals regulation, including UK REACH. We will provide a summary of the responses during 2025.

“Country specific” exposure information?





Chemicals

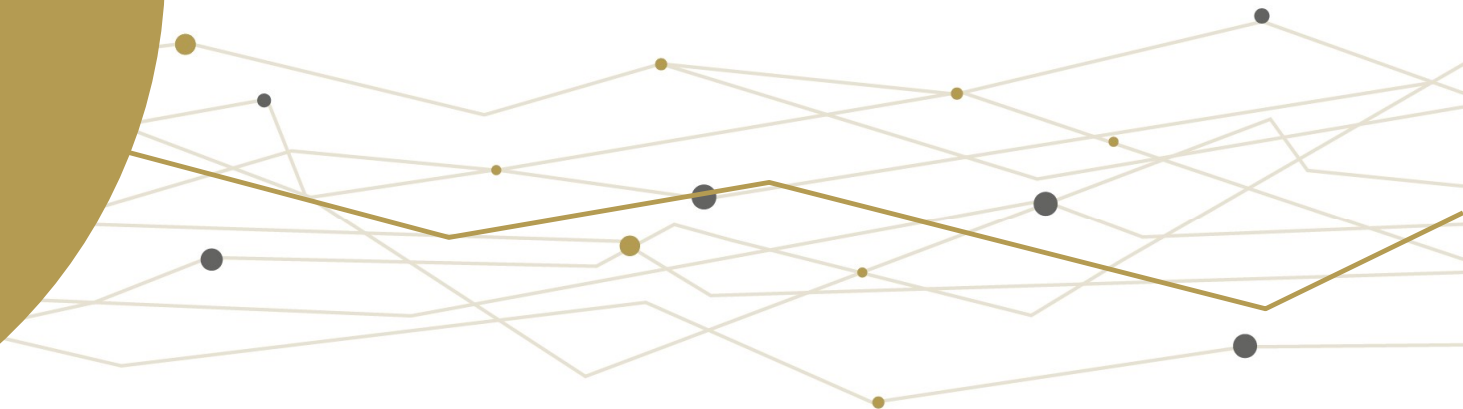


Biocides



Crop protection

Wrap-up



Wrap-up – human health exposure prediction

- ▶ Tier 1 standard tools differ / not necessarily available.
- ▶ Refinement requires detailed knowledge of the use (pictures? / videos?).
- ▶ Stay flexible.
- ▶ Be investigative.
- ▶ Acceptance of operator exposure data not guaranteed.
- ▶ Updating existing indicative values considering newer data would be very beneficial.
- ▶ Increased demand of exposure assessors not unlikely.

Any questions?



Think globally, act locally - your local contact



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