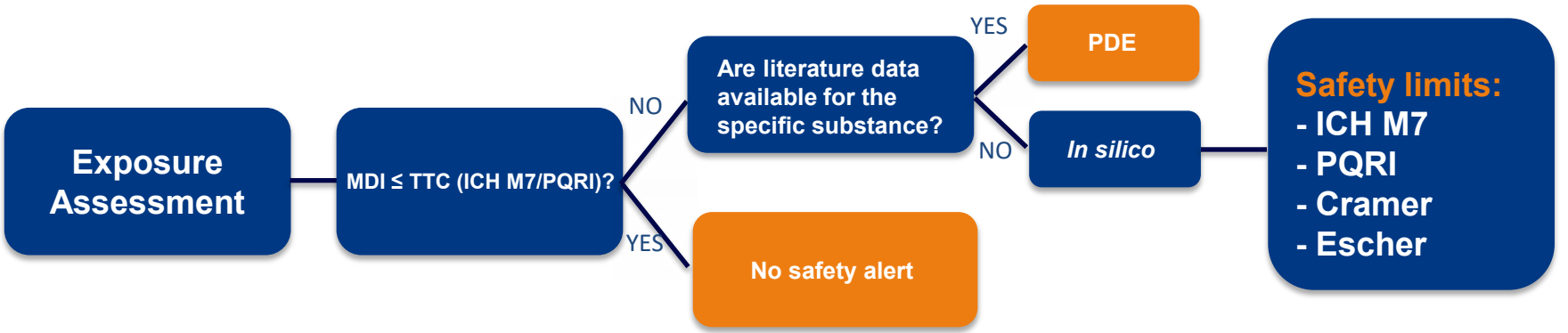
II. Determination of PDE values

Eurofins approach to Toxicological Risk Assessment



1. The safe threshold value: Permitted Daily Exposure (PDE)

The PDE represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime.

ICH guideline Q3D on elemental impurities

PDEs for elemental impurities

ICH guideline Q3C on impurities: guideline for residual solvents

PDEs for ICH Q3C residual solvents

EMA/CHMP/ CVMP/ SWP/169430/2012

How to set PDEs

2.PDE: how is it calculated?

PDE

- Hazard identification by reviewing all relevant data
- Identification of “critical effects”
- Determination of the no-observed-adverse-effect level (NOAEL) of the findings that are considered to be critical effects
- Use of several adjustment factors to account for various uncertainties

$$PDE = \frac{NOAEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

PDE: how is it calculated?

Hazard Identification

Qualitative appraisal of the inherent property of a substance to produce adverse effects.

Data for hazard identification would include:

- Non-clinical pharmacodynamic data;
- Repeat-dose toxicity studies;
- Carcinogenicity studies;
- *In vitro* and *in vivo* genotoxicity studies;
- Reproductive and developmental toxicity studies;
- Clinical data (therapeutic and adverse effects).

Identification of "critical effects"

Critical effects would include the most sensitive indicator of an adverse effect seen in non-clinical toxicity studies unless there is clear evidence (e.g. from mechanistic studies, pharmacodynamic data etc.) that such findings are not relevant to humans or the target animal. A critical effect would also include any clinical therapeutic and adverse effect.

PDE: how is it calculated?

Establishing the NOAEL (s) : No-Observed-Adverse-Effect-Level

For all critical effects identified, a NOAEL should be established.

The NOAEL is the highest tested dose at which no “critical” effect is observed.

→The NOAEL is dependent upon the selection of dose levels when the study was designed and on the ability of the study to detect adverse effects.

→If the critical effect is observed in several animal studies, the NOAEL occurring at the lowest dose should be used for calculation of the PDE value.

→If no NOAEL is obtained, the lowest-observed-adverse-effect level (LOAEL) may be used.

PDE: how is it calculated?

Establishing the NOAEL (s) – adverse effect

Adverse effect: Change in the morphology, physiology, growth, development, reproduction, or life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.

http://www.inchem.org/documents/harmproj/harmproj/harmproj1.pdf

The data for hazard identification (tox. studies) can be retrived from various databases, such as:

- Toxplanet
- PubChem
- PubMed
- OECD
- FDA
- COSMOS

PDE: how is it calculated?

Application of adjustment factors

The PDE is derived by dividing the NOAEL for the critical effect by various adjustment factors (also referred to as safety-, uncertainty-, assessment- or modifying factors) to account for various uncertainties and to allow extrapolation to a reliable and robust no-effect level in the human or target animal population.

F1
- A factor (2 to 12) to account for extrapolation between species;
- Rats, mice, dogs, rabbits, monkeys, others.

F2
- A factor of 10 to account for variability between individuals;
- genetics, age, sex, physiologic/pathologic conditions, diseases.

F3
- A factor 10 to account for repeat-dose toxicity studies of short duration;
- i.e. less than 4-weeks.

F4
- A factor (1-10) that may be applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity;

F5
- A variable factor that may be applied if the no-effect level was not established. When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities EMA/CHMP/CVMP/SWP/169430/2012

PDE: how is it calculated?

Weight adjustment

"The weight adjustment assumes an arbitrary adult human body weight for either sex of **50 kg**. This relatively low weight provides an additional safety factor against the standard weights of 60 kg or 70 kg that are often used in this type of calculation"

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ich-guideline-q3c-r8-impurities-guideline-residual-solvents-step-5_en.pdf

"If the product information for the next medicinal product to be manufactured expresses the daily dose on a per patient basis rather than on a mg/kg bw basis, a standard body weight of **50 kg** should be used for human medicinal products."

EMA/CHMP/CVMP/SWP/169430/2012

PDE: how is it calculated?

Extrapolation to other routes of administration

In the absence of data and/or where data are available but not considered sufficient for a safety assessment for the parenteral and or inhalation route of administration, modifying factors based on oral bioavailability were used to derive the PDE from the oral PDE:

Oral bioavailability <1%: divide by a modifying factor of 100	**Oral bioavailability = 1% and <50%: divide by a modifying factor of 10**	**Oral bioavailability =50% and <90%: divide by a modifying factor of 2**	**Oral bioavailability = 90%: divide by a modifying factor of 1**

NB: Where oral bioavailability data or occupational inhalation exposure limits were not available, a calculated PDE was used based on the oral PDE divided by a modifying factor of 100.

ICH guideline Q3D (R2) on elemental impurities

PDE: how is it calculated?

General considerations

$$PDE = \frac{NOAEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

- It is considered pragmatic that PDEs should be derived assuming human exposure. The level of contamination that can be accepted is then calculated from the human PDE, even when the product that will be contaminated is a veterinary medicinal product;
- PDE should be calculated on a mg/kg bw basis;
- If several critical effects have been identified resulting in calculation of more than one PDE value, a decision with respect to the most appropriate PDE to be used for the cleaning validation process should be made with an appropriate justification. Usually, by default the lowest PDE value will be used.

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3.PDE: Specific Considerations

Active substances with a genotoxic potential

For genotoxic active substances for which there is no discernible threshold, it is considered that any level of exposure carries a risk.

A pre-defined level of acceptable risk for non-threshold related genotoxicants has been established in the EMA Guideline on the Limits of Genotoxic Impurities in the form of the **Threshold of Toxicological Concern (TTC) of 1.5 µg/person/day.**

Hence, in the case of residual active substances without a threshold, a limit dose of 1.5 µg/person/day may be applied.

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PDE: Specific Considerations

Active substances with a highly sensitising potential

Drug-induced immune-mediated hypersensitivity reactions may develop in sensitive individuals.

Classification of an active substance or medicinal product with a high sensitising potential should consider whether the substance shows a high frequency of sensitising occurrence in humans; or a probability of occurrence of a high sensitisation rate in humans based on animal data or other validated tests. Severity of these reactions should also be considered and should be included in a weight of evidence assessment.