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Nuovi trend in tossicologia regolatoria: si conclude l'era Cramer?

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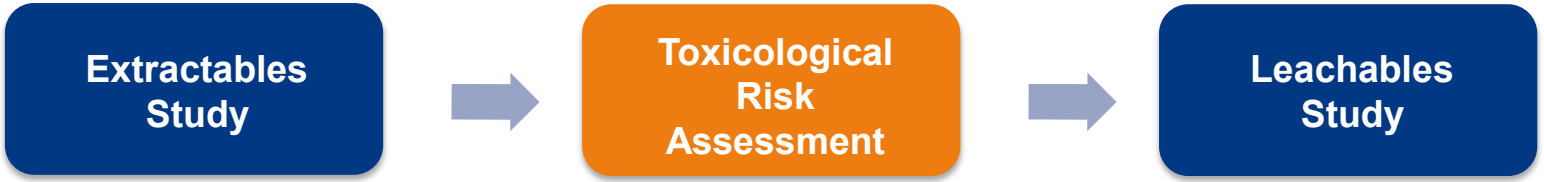
Extractables & Leachables



ICH Q3E : Guideline for Extractables and Leachables (E&L) → Coming Soon 2023

- **Extractables** are chemical substances that can migrate from the materials into solvents under exaggerated conditions of time and temperature;
- **Leachables** are compounds that actually migrate into a product formulation under normal storage or during the manufacturing conditions.

Toxicological Risk Assessment

Act of determining the potential of a chemical to elicit an adverse effect based on a specified level of exposure.

Data generated from an extractable study should be evaluated to determine the potential toxicological concern of the extracted compounds

"Everything is poison,
there is poison in everything.
Only the dose makes a thing not a poison."

(Paracelsus, 1493-1541)

Toxicological Risk Assessment

Systematic scientific evaluation of the **potential adverse health effects** resulting from **human exposure to hazardous agents or situations**. Risk assessments require an integration of both qualitative and quantitative data.

All toxicological risk assessments are composed by four steps:

1) **Hazard Identification;**
2) **Exposure Assessment;**
3) **Toxicity Assessment;**
4) **Risk Characterization.**

1. Hazard Identification

This section of the risk assessment identifies the chemicals that patients may come into contact with. These chemicals are known as **"Chemicals of Potential Concern"** (COPC).

In case of E&L the COPC are the **Extractables or Leachables** compounds released from the packaging/process component

2. Exposure Assessment

Maximum amount of extractable that a patient can take daily. Calculated based on the posology of the drug product.

$$\textbf{Maximum daily Intake}\ \left(\frac{\mu g}{day}\right) = \text{Released Amount}\left(\frac{\mu g}{packaging}\right) \times N\left(\frac{packaging}{day}\right)$$

Threshold of Toxicological Concern

The Threshold of Toxicological Concern (TTC) approach is a risk assessment tool establishing that for human exposure threshold values of chemicals below TTC, there is a very low probability of adverse effects to human health.

A “less than lifetime exposure” (LTL) concept

Duration of treatment	≤ 1 month	> 1 - 12 months	> 1 - 10 year	> 10 years to lifetime
Total Daily intake [µg/day]	120	20	10	1.5

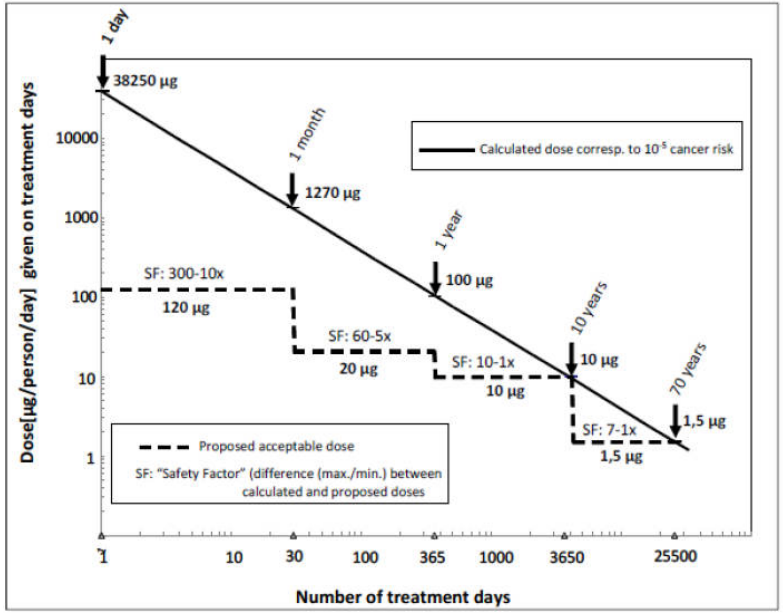
“M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk”, May 2015.

Threshold of Toxicological Concern

The TTC of **1.5 µg/day** is considered to be protective for a lifetime of daily exposure (cancer risk of < 1 in 100.000 over a lifetime of exposure)

Haber's rule: concentration (C) x time (T) = a constant (k) → The carcinogenic effect is based on both dose and duration of exposure.

Linear relationship between the amount of daily intake of a mutagenic impurity corresponding to a 10^{-5} cancer risk and the number of treatment days.



PQRI

The Product Quality Research Institute (PQRI) Toxicology Team established a threshold for sensitizers of 5 µg/day, proposed to develop scientifically-justified thresholds for leachables in parenteral and ophthalmic drug products

"SAFETY THRESHOLDS AND BEST PRACTICES FOR EXTRACTABLES AND LEACHABLES IN ORALLY INHALED AND NASAL DRUG PRODUCTS,http://pqri.org/wpcontent/uploads/2015/08/pdf/LE_Recommendations_to_FDA_09-29-06.pdf"

→ **FDA requirement**

Screening with TTC

Maximum Daily Intake **below** the TTC → **No further evaluation**, the extracted compounds are considered to pose a negligible risk for human safety.

Maximum Daily Intake **above** the TTC → **further toxicological assessment** is advisable for that compound in order to elucidate its risk for human safety.

3. Toxicity Assessment

Step in the risk assessment wherein the scientific information concerning the **toxicological properties** of the COPC is detailed.

The toxicological profile of a substance includes information on:

- Systemic toxicity after single and repeated administration;
- Local tolerance including irritating potential and skin sensitization;
- Reproductive/developmental toxicity;
- Genotoxicity/mutagenicity;
- Carcinogenicity;
- Toxicokinetics.

Based on these data, compound-specific limits or **permitted daily exposure (PDE)** can be established.

4. Risk characterization

The calculated worst case exposure of patients for each compound is compared to the toxicological profile and derived PDE or, if no appropriate data are available to determine a PDE, to generic default thresholds, such as the threshold of toxicological concern (TTC).

$$\text{Margin Of Safety (MOS)} = \frac{\text{Final proposed PDE } \left(\frac{\mu g}{day}\right) \text{ or Final Proposed TTC } \left(\frac{\mu g}{day}\right)}{\text{Maximum Daily Intake } \left(\frac{\mu g}{day}\right)}$$

If MOS ≥ 1 → No Toxicological Concern
If MOS < 1 → Toxicological Concern