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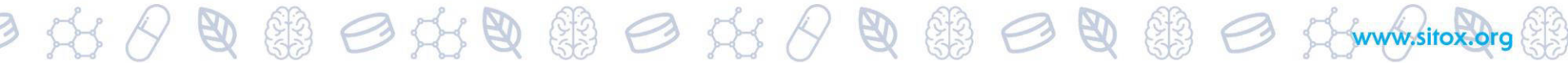
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BOLOGNA 20-22 Febbraio 2023

Pericolo, rischio e rapporto rischio-beneficio

III. Alternative TTC values - ELSIE approach



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The Extractables and Leachables Safety Information Exchange Consortium (ELSIE)

PDA Journal
of Pharmaceutical Science and Technology

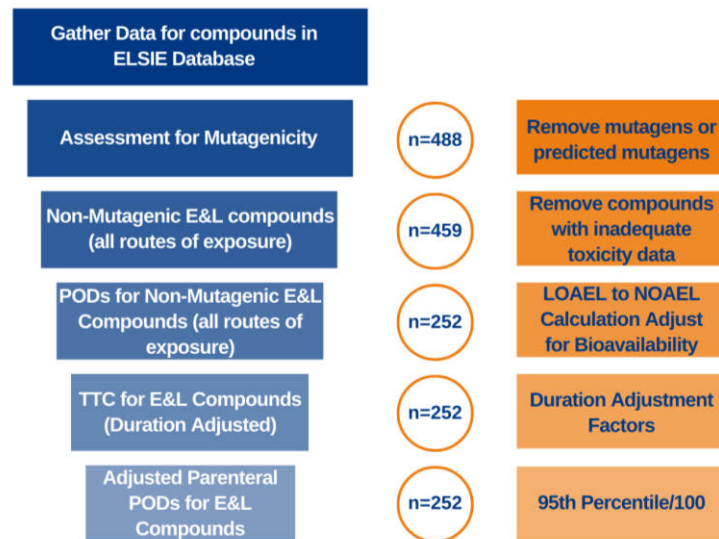


Development of Duration-Based Non-Mutagenic Thresholds of Toxicological Concern (TTC) Relevant to Parenteral Extractables and Leachables (E&Ls)

Melisa J. Masuda-Herrera, Joel P. Bercu, Thomas H. Broschard, et al.

PDA Journal of Pharmaceutical Science and Technology 2022,
Access the most recent version at [doi:10.5731/pdajpst.2021.012693](https://doi.org/10.5731/pdajpst.2021.012693)

- ELSIE Consortium was established in 2007;
- It comprised together leading scientists and industries of biotechnology, pharmaceutical and medical devices to share safety information on extractables and leachables;
- “We do not compete on safety”.



Development of Duration-Based Non-Mutagenic Thresholds of Toxicological Concern (TTC) Relevant to Parenteral Extractables and Leachables (E&Ls).
PDA Journal of Pharmaceutical Science and Technology January 2022

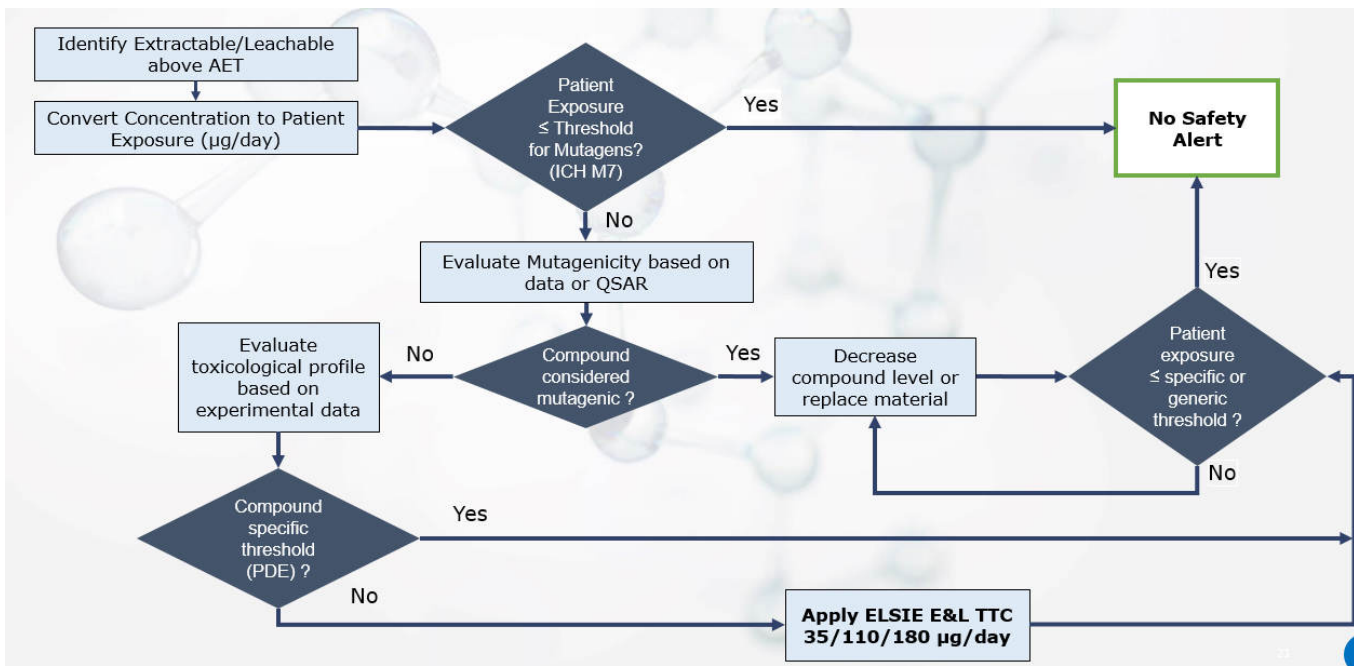
ELSIE TTC

- Organic Parenteral TTCs for Non-Mutagenic Impurities

| | ≤1 year | ≤10 years | >10 years to lifetime |
|---|---------|-----------|-----------------------|
| Parenteral TTC [$\mu\text{g}/\text{day}$] | 180 | 110 | 35 |

Development of Duration-Based Non-Mutagenic Thresholds of Toxicological Concern (TTC) Relevant to Parenteral Extractables and Leachables (E&Ls). PDA Journal of Pharmaceutical Science and Technology January 2022

ELSIE workflow



Eurofins Approach



TTC for Non-Mutagenic Impurities Cramer Classes

- **Class I** contains substances of simple chemical structure with known metabolic pathways and innocuous end products which suggest a low order of oral toxicity.
- **Class II** contains substances that are intermediate. They possess structures that are less innocuous than those in Class I but they do not contain structural features that are suggestive of toxicity like those in Class III.
- **Class III** contains substances with a chemical structures that permit no strong initial impression of safety and may even suggest a significant toxicity.

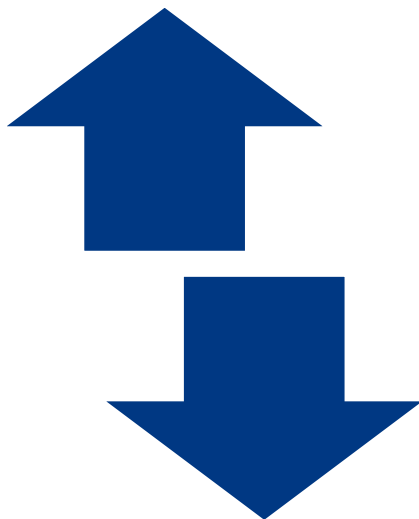
| Type of TTC value | TTC value in $\mu\text{g}/\text{kg}$ bw/day | TTC value in $\mu\text{g}/\text{day}$ (50kg person) |
|-------------------|---|---|
| Cramer Class III | 1.5 | 75 |
| Cramer Class II | 9 | 450 |
| Cramer Class I | 30 | 1500 |

TTC for Non-Mutagenic Impurities Escher Classes

- Cramer Classes were developed considering oral exposure data. The RepDose database of Fraunhofer ITEM, Germany gives information on 650 substances, including 203 substances for which administration was by the inhalation route (Escher et al., 2010). The latter were reduced to 136 substances after exclusion of those with structural alerts for genotoxicity, and from these they derived systemic TTC values of 180 $\mu\text{g}/\text{person}$ per day for substances in Cramer Class I and 4 $\mu\text{g}/\text{person}$ per day for substances in Cramer Class III.

| Type of TTC value | TTC value in $\mu\text{g}/\text{person}/\text{day}$ | TTC value in $\mu\text{g}/\text{day}$ (50kg person) |
|--------------------------------------|---|---|
| Cramer Class III and Cramer Class II | 4 | 3 |
| Cramer Class I | 71 | 59 |

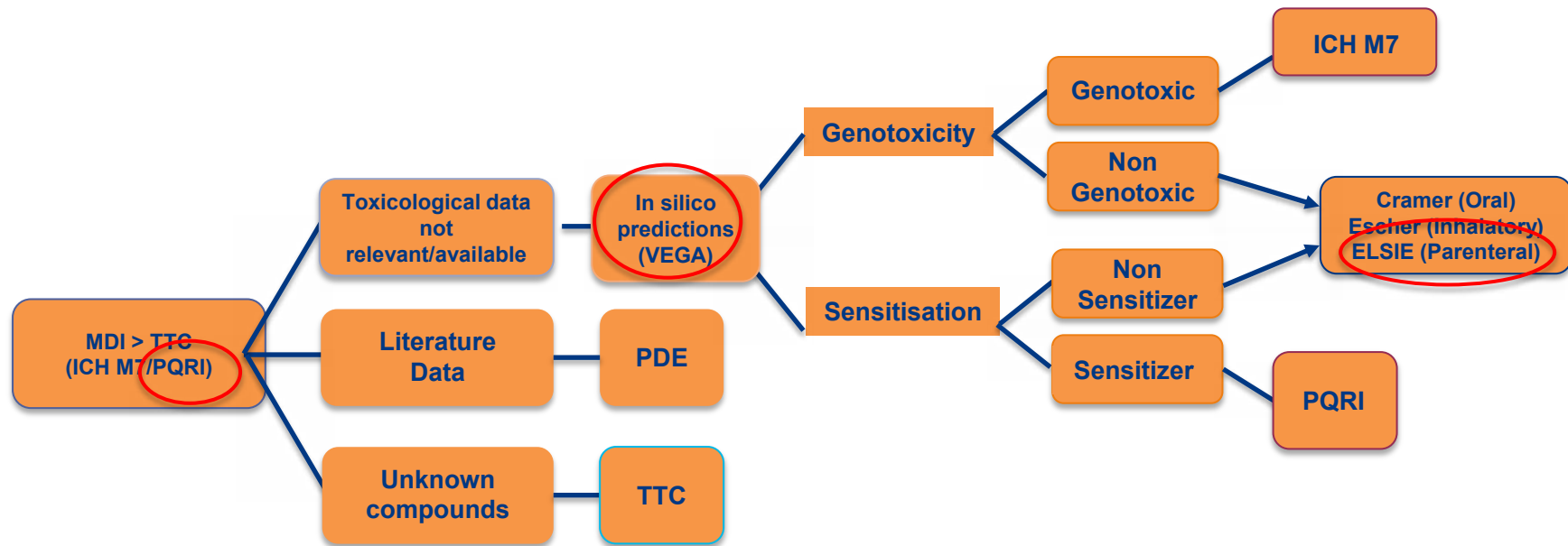
Strong points vs Open points



- ELSIE si basa su un E&L database
- ELSIE è specifico per la via di somministrazione parenterale
- Toxicity assessment specifico

- Sensibilizzazione e PQRI?
- Predizioni *in silico*?

An hybrid approach





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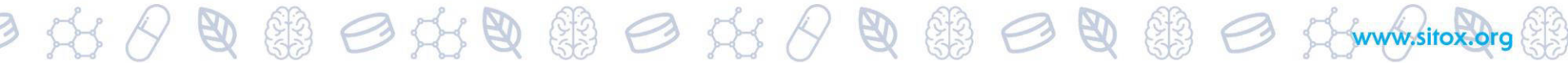
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...quindi si conclude l'Era di Cramer?



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Paolo Pescio

Senior Scientific
Director and ERT



Eleonora Lostaglio

Toxicology
Consultant



Matilde Ciaroni

Toxicology
Consultant



Ilaria Coccoglioni

Toxicology
Consultant

GRAZIE PER L'ATTENZIONE

ConsultingItaly@eurofins.com