



# Evaluating the utility of the Threshold of Toxicological Concern (TTC) and its exclusions in the safety assessment of extractable substances from medical devices

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## OBJECTIVES

- A large inventory of 45K substances (LRI set) were profiled through the Kroes TTC decision module within Toxtree 3.1 to assign substances to their respective TTC category
- In the category of substances for which the TTC is not applicable, examination of the substances uncovered a number of issues.

## APPROACH

- Assess the relevance and coverage of representatives from the medical device chemical space relative to a large inventory of 45K substances covering multiple industrial sectors,
- Evaluate the exclusion rules as implemented in the Kroes workflow within the Toxtree software implementation.

## MAIN RESULTS

- Profiled LRI against representative medical device extractables from the ELSIE data. 32 ToxPrints were enriched in the ELSIE dataset.
- New set of rules developed to better discriminate essential metals and inorganics
- Refined TTC exclusion rules

## IMPACT

- This study demonstrated the importance of evaluating the software implementation of established TTC workflows
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# Evaluating the utility of the TTC and its exclusions in the safety assessment of extractable substances from medical devices

## OBJECTIVES

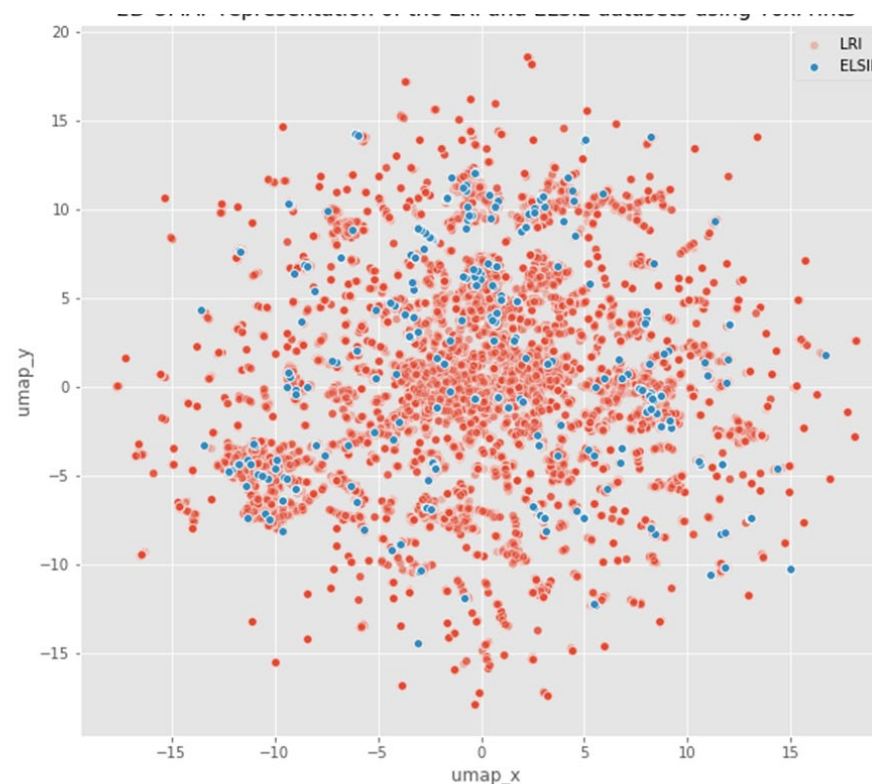
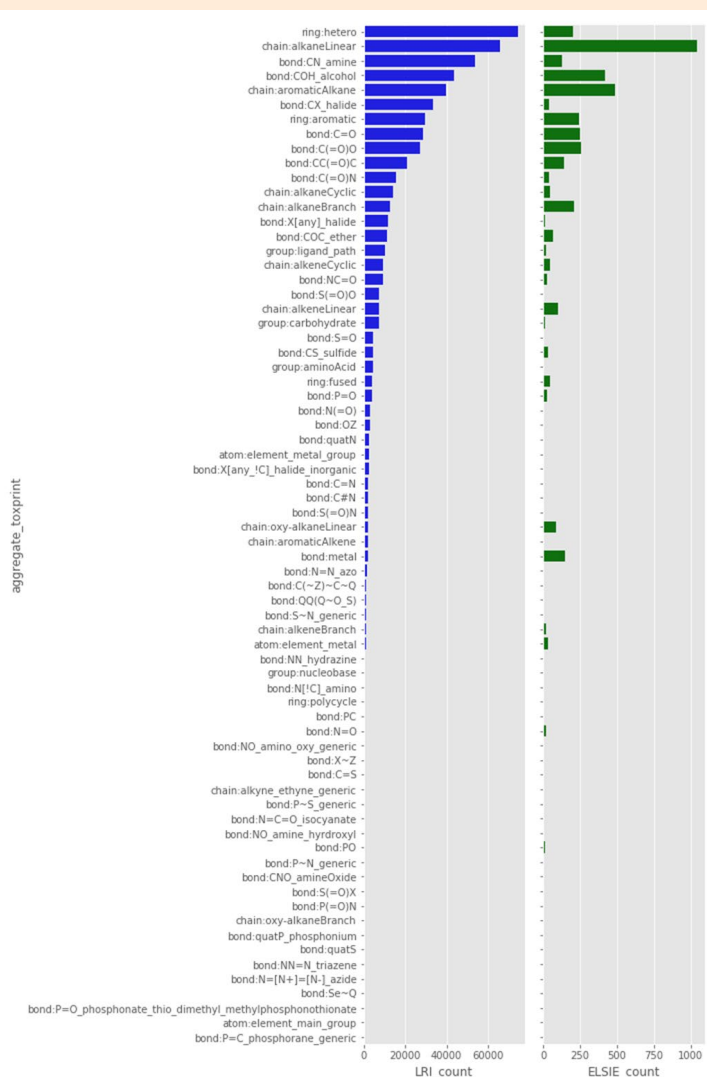
This case study had 3 main objectives:

- 1) to assess the relevance and coverage of representatives from the medical device chemical space (the dataset utilised is known as ELSIE, from the Extractables and Leachables Safety Information Exchange) relative to a large inventory of 45K substances covering multiple industrial sectors,
- 2) to perform a closer evaluation of the exclusion rules as implemented in the Kroes workflow within the Toxtree software implementation and,
- 3) Apply the revised TTC exclusion rules to the ELSIE dataset.

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## MAIN RESULT

- Profiling the LRI set against the ELSIE dataset based on Level 2 ToxPrints
- Uniform Manifold Approximation and Projection (UMAP) using ToxPrints



# Evaluating the utility of the TTC and its exclusions in the safety assessment of extractable substances from medical devices

## MAIN RESULTS

Profiled the LRI dataset (45,017 substances) through the Kroes TTC decision tree module within Toxtree v3.1, 4002 were determined 'Not appropriate for TTC'

| Exclusion reason         | Number of substances |
|--------------------------|----------------------|
| Yes to Q1                | 3759                 |
| High Potency Carcinogens | 241                  |
| Steroid                  | 2                    |

Toxtree includes P as an essential metal, does not include Si (which should be an exclusion) and includes B which is not a metal. Organic salts where the counter ion is an essential metal are permitted to be included for TTC.

A new set of rules were developed a) to identify the presence of a metal atom and distinguish it from an essential metal that was a salt and b) to identify inorganic substances that did not contain C such as inorganic phosphorus.

If the excluded substances were reconsidered, then of the 4002 substances, only 639 were found to be inorganic and not appropriate for TTC. 2220 substances were actually metal salts where the metal was an essential metal and could therefore be considered for TTC. The remaining 1143 were still not applicable for TTC due to the substances being dioxin-like, a steroid or a high potency carcinogen.

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## MAIN RESULTS

- 241 substances were tagged as High Potency Carcinogen (HPC). The expectation was that existing structural alerts for genotoxicity such as the Istituto Superiore di Sanita (ISS) alerts already implemented as a module in Toxtree were the same alerts used to designate a substance as a HPC.
- For the 241 substances tagged as HPC, 204 substances were flagged due to possessing a N-nitroso alert and 8 for containing azoxy alerts. However, 28 substances fired other genotoxicity structural alerts (aromatic nitro, aliphatic nitro, hydrazine, aromatic diazo) and 1 substance did not flag any alerts.
- Within the Kroes TTC decision tree, there was no alert for benzidine, the aflatoxin like substance only identified aflatoxin itself and azoxy and N-nitroso flags were represented as generic functional group flags rather than specific structural alerts. A new set of queries were created to better capture the HPC alerts using SMARTS patterns - either created manually or extracted from existing ISS structural alerts. Seven SMARTS patterns were created or extracted from existing alerts for 'aflatoxin-like' substances, 5 SMARTS patterns were created for Azoxy substances, 2 SMARTS for Nitroso- substances and 1 pattern for Benzidine.



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## MAIN RESULTS

- Q1Y also addresses substances that are dioxin-like (DLC) including polyhalogenated - dibenzodioxins, dibenzofurans and biphenyls. It was not possible to elucidate how the Kroes TTC decision tree was identifying these substances. New SMARTS patterns were constructed to capture these substances.
- The International Organization for Standardization (ISO) Technical Specification 21726 includes a recommended list of substances that would be tagged as 'cohort of concern' (CoC) and hence not appropriate for application of TTC approach for assessing biocompatibility of medical device constituents. In addition to the inorganic substances, steroids, DLCs and HPCs, a number of additional alerts have been proposed.
- Examples of CoCs include azo compounds, strained heteronuclear rings, alpha-nitro furyl compounds, hydrazines, triazenes, azides, organophosphorus compounds and polycyclic amines.
- A list of COC were compiled based on DNA alerts proposed in Enoch et al (2011), the ISS alerts, alerts published on the OCHEM Toxalerts website as well as the revised organophosphate alerts from Nelms et al (2019).

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## MAIN RESULTS

| TTC category   | Number of substances |
|--|----------------------|
| Inorganic  | 1012                 |
| CoC  | 4407                 |
| Substances presenting a genetox alert (including carbamates/OPs) | 20,672               |
| Cramer class applicable  | 18,947               |

- With the revised set of genotoxicity alerts, the number of substance presenting an alert was much higher. Further evaluation of the genotoxicity structure alerts used and their specificity is a key next step.

# Evaluating the utility of the TTC and its exclusions in the safety assessment of extractable substances from medical devices

## IMPACT/SIGNIFICANCE

- A closer examination of substances identified as Not Appropriate for TTC' by the Toxtree software was made and uncovered a number of issues.
- This study demonstrated the importance of evaluating the software implementation of established TTC workflows.