Analysis of the sensitisation potential of extractables and leachables in parenteral pharmaceutical products

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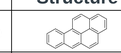
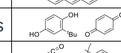
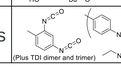
Introduction

- Extractables and leachables (E&Ls) are chemicals which can potentially migrate from container closure systems or manufacturing components into drug products, under exaggerated or normal conditions, respectively. Leachables should undergo a toxicological risk assessment (TRA) which may include potential to induce sensitisation.[1,2]
- This study analysed E&L sensitisation prevalence and potency, to inform a risk-based approach to prevent potential induction of sensitisation from low-level parenteral E&Ls.[3]
- There are no approved assays to identify systemic sensitisation. The local lymph node assay (LLNA) has the potential to detect both dermal and respiratory sensitisers, based on a common mechanism of activation and proliferation of T cells in the lymph nodes.
- Dermal sensitisation data can be a conservative indication of systemic sensitisation potential, by considering activation of the immune system via any route of administration.

Most E&Ls are not strong/extreme sensitisers

- All positive sensitisation data was reviewed so that each chemical could be assigned an ECETOC potency category of either weak, moderate, strong or extreme.[5]
- Most E&Ls with data are **non-sensitisers (n=308, 76%)**, while sensitising E&Ls are more likely to be **weak/moderate (n=78, 19%)** than **strong/extreme (n=21, 5%)**.

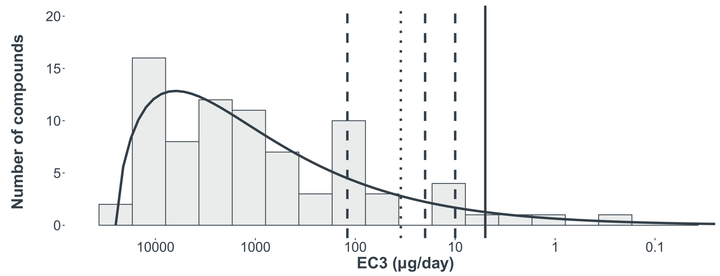
The eight most potent extremely sensitising E&Ls in the dataset

Name	Structure	LLNA EC3 (%)	Comments
Benzo[a]pyrene		0.0009	The EC3 values are less reliable as they have been extrapolated from the data. They are also not commonly seen E&Ls.
(Hydro)quinones		0.005-0.0099	
Iso(thio)cyanates	 (Plus TDI dimer and trimer)	0.028-0.052	Isocyanates are very prone to hydrolysis[6] so are unlikely to be stable leachables.

Existing safety thresholds are highly protective

- The potency values were converted to a dose per day unit[2,3] and plotted as a histogram, before a gamma curve was fit to the data to describe the potency distribution.[3]
- Five existing safety thresholds were plotted,[1,8,9] including some less-than-lifetime (LTL) durational limits, and the percentage of the distribution covered by each was calculated.
- By accounting for prevalence of sensitisation in E&Ls (24.3%), the probability of any E&L being less potent than each safety threshold was shown to be very high (95-99%).
- This analysis is conservative as it does not differentiate between extractables and leachables, but this is a critical distinction to make when conducting a chemical TRA.

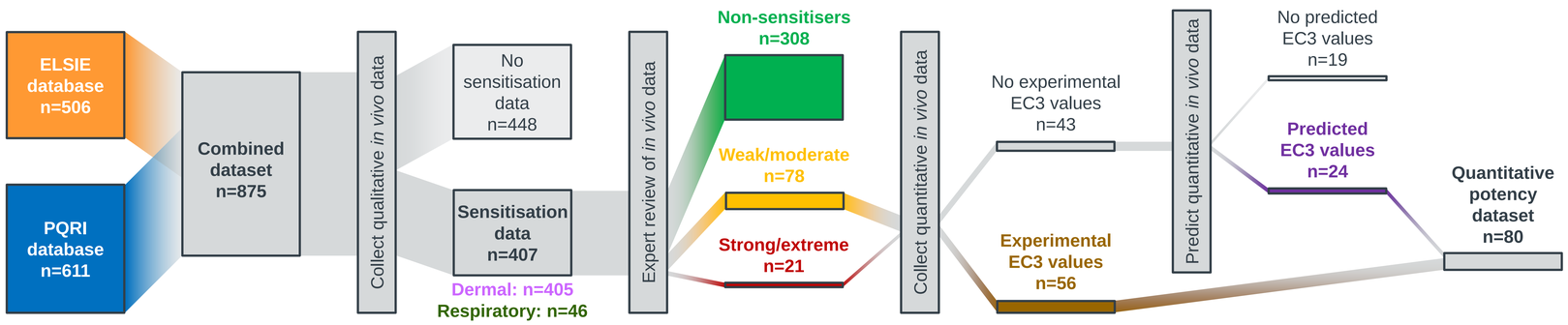
Distribution of E&L potency values and comparison to existing safety thresholds



Key	Safety threshold	Value	Protectiveness[a]
———	PQRI qualification threshold[1]	5 µg/day	99%
– – –	ICH M7 mutagenicity TTC (LTL: 1-10 years)[8]	10 µg/day	98%
– – –	ICH M7 mutagenicity TTC (LTL: 1-12 months)[8]	20 µg/day	98%
· · · · · ·	ELSIE non-mutagenic systemic toxicity TTC[9]	35 µg/day	97%
– – –	ICH M7 mutagenicity TTC (LTL: <1 month)[8]	120 µg/day	95%

[a] Probability that an E&L will be either non-sensitising or sensitising but less potent than the safety threshold.

E&Ls with both qualitative and quantitative sensitisation data have been identified from two databases



Sensitisation data is available for >400 E&Ls

- 875 E&L structures were sourced from the **ELSIE** and **PQRI** databases.[1,3]
- Sensitisation data for 407 E&Ls was found in Vitic (v5.0.0, 2022.1.0 DB),[4] OECD QSAR Toolbox (v4.5), REACH dossiers, ELSIE knowledge base, and the scientific literature.
- Most chemicals with sensitisation data were tested via the **dermal route (n=405, >99%)** in various species, while a few had human data via the **respiratory route (n=46, 11%)**.

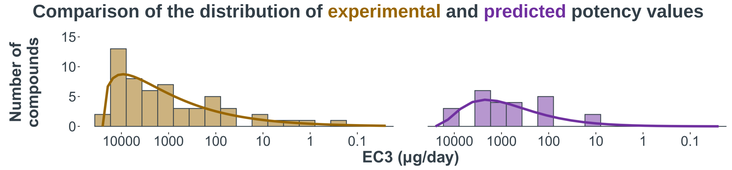
Species distribution of the available dermal and respiratory sensitisation data

Sensitisation endpoint	Species					
	Guinea pig	Human	Mouse	Other	Multiple	**Total**
Dermal	181	52	49	4	119	**405**
Respiratory	0	46	0	0	0	**46**

In silico potency predictions are conservative

- Potency predictions from a k-NN model[7] in Derek Nexus (v6.2.1, 2022 2.0 KB)[4] were used for E&L sensitisers where experimental potency values were not available.
- These predicted values occupy a more potent distribution than the experimental values.

Comparison of the distribution of experimental and predicted potency values



- 91% of the experimental sensitisers which are assigned a potency value by Derek Nexus are predicted to be in the correct or a more potent ECETOC potency category.

Conclusions

- Very few of the over 400 E&Ls analysed in this study are strong/extreme sensitisers.
- E&L sensitisation potency can be conservatively predicted *in silico* when data is lacking.
- Analysis of the potency and prevalence of sensitisers in the available dataset identified various safety thresholds to be ≥95% protective against the induction of sensitisation.
- This supports the use of ICH M7 and ELSIE thresholds as the safety concern threshold for analytical testing of E&Ls and when establishing the analytical evaluation threshold.

References

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