Best practice for conducting expert review of sensitisation data and predictions

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❑ Introduction

Skin sensitisation is a toxicity endpoint which is relevant for many industries that use or produce chemicals, such as cosmetics, industrial chemicals, and pharmaceutical impurities including extractables and leachables (E&Ls). It is important to evaluate the sensitisation potential of chemicals accurately, including an assessment of potency. A key step when interpreting both data and predictions is to perform expert review, as this will increase confidence in the assessment and provide additional support when resolving conflicting or inconclusive pieces of evidence. This study sought to highlight some of the key principles of such an expert review and to capture these in best practice, to help accessors to apply methods and reasoning in a consistent manner which can help with regulatory acceptance. A step wise systematic approach was adopted to assess the sensitisation hazard and potency of the compounds by applying expert review to both data and predictions.

Chemicals to assess

Best practice framework to assess skin sensitisation of chemicals, such as:

- Cosmetics
- Industrial chemicals
- Pharmaceutical impurities
- Extractables and leachables (E&Ls)

Data

Vitic:
26,020 *in vivo* records for 5970 substances

Factors impacting confidence in the data:

- ✓ Result generated from recommended assay
- ✓ Negative results tested to a suitable maximum concentration
- ✓ Potency classification → Expert review is finalised
- X No potency classification → Move to (Q)SAR

(Q)SAR

Derek Nexus:
105 skin sensitisation alerts, 19 HPC alerts, kNN EC3 model

Factors impacting confidence in the prediction:

- ✓ Identify unsuitable analogues used for potency prediction[3] based on mechanistic knowledge[4]
- ✓ Analyse chemicals in a High Potency Category (HPC) to identify any mitigating features[5]
- ✓ Perform read-across for low confidence negative predictions[2]

Expert review

Outcome of expert review:

- ✓ Increased confidence in the assessment of both sensitisation hazard and potency.
- ✓ Provide additional support when resolving conflicting or inconclusive pieces of evidence.
- ✓ Likely to support regulatory acceptance.

Sensitisation classification

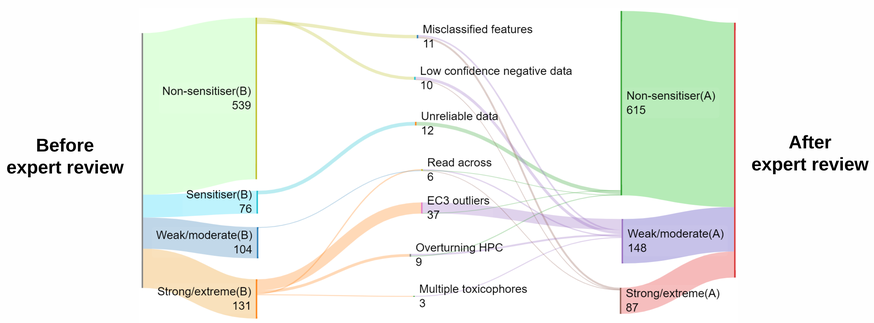
Non-sensitising
EC3 > 100% → Non-sensitiser

Weak/moderate[6]
EC3: 10-100% → Weak, EC3: 1-10% → Moderate

Strong/extreme[6]
EC3: 0.1-1% → Strong, EC3 < 0.1% → Extreme

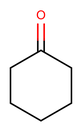
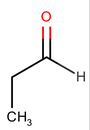
❑ Analysis of an E&L dataset

- An E&L dataset of **850 compounds** was compiled from the published ELSIE and PQRI databases.[1]
- Prior to review **850 chemicals** were classified conservatively using data and *in silico* predictions. **452 chemicals** were reviewed, focusing on those with experimental data, positive *in silico* predictions and low confidence negative (chemicals with misclassified/unclassified feature) *in silico* predictions[2].
- After expert review, the classification of **88 chemicals** altered, with **66 chemicals** being given a less potent classification and **22 chemicals** being given a more potent classification. As only **~10 %** of classifications changed upon expert review, this highlights the reliability of the data and predictions used in the assessment and that expert review will increase the confidence in the safety assessments.



Common reasons for changing the classification

❑ Case studies

Chemicals to be assessed	Prior to expert review: Classification based on the data from Vitic	Prior to expert review: Classification based on the prediction from Derek	Review experimental data	Review *in silico* prediction	Potency assessment after expert review
 **Cyclohexanone, CAS:108-94-1**	**Sensitiser**	**Non-sensitiser**	• Positive GPMT studies were observed for cyclohexanone resins. A resin based on cyclohexanone (Laropal K 80) was tested negative → **Unreliable data**. • **Two reliable negative** GPMT study record tested up to 100% induction concentration following standard protocol. [7]	• Confident **negative** prediction, supports negative experimental data.	**Non-sensitiser**, overturned classification using confident experimental data. Conclusion also supported by QSAR evidence.
 **Propanal, CAS: 123-38-6**	**Inconclusive**	**Strong/extreme**	• **Inconclusive** Buehler test study. • Additional **negative** LLNA study located in ECHA REACH dossier but tested only up to 10% induction concentration.[7] • Classification can't be assigned accurately.	• **Sensitise**r based on *in silico* structural alert predicting Schiff base mechanism. • Potent EC3 prediction driven by nearest neighbours containing multiple reactive sites binding to proteins. • **Outliers** are removed from the EC3 calculation because query compound has only one reactive site.	**Weak/moderate,** based on kNN model, downgraded from strong/extreme after removal of irrelevant analogues. Conclusion also supported by limited negative experimental data.

❑ Conclusions

- This analysis has identified key best practices for evaluating the skin sensitisation potential using historical data and *in silico* predictions.
- This approach is widely applicable to substances which require an assessment of sensitisation potential, such as cosmetic ingredients within a Next Generation Risk Assessment, E&Ls and chemicals which need to undergo an occupational toxicology assessment.
- For the E&L dataset, ~10% of the original classifications were altered and confidence in the classifications could be increased by expert review. This highlights that the data from Vitic and predictions from Derek can provide reliable information for skin sensitisation assessments and the value expert review brings to decision making for chemical safety assessments.

❑ References

1) PQRI dataset - PQRI, Safety thresholds and best demonstrated practices for extractables and leachables in parenteral drug products (intravenous, subcutaneous, and intramuscular), **2021;** ELSIE dataset - Parris et al., *PDA J. Pharm. Sci. Technol.*, **2023**.
2) Chilton et al., Making reliable negative predictions of human skin sensitisation using an *in silico* fragmentation approach, *Regul. Toxicol. Pharmacol.*, **2018**, 95, 227.
3) Chilton et al., An *in silico* workflow for assessing the sensitisation potential of extractables and leachables, *Comput. Toxicol.*, **2023**, 27, 100275.
4) Canipa et al., A quantitative *in silico* model for predicting skin sensitization using a nearest neighbours approach within expert-derived structure–activity alert spaces, *J. Appl. Toxicol.*, **2017**, 37, 985.
5) Chilton et al., Updating the Dermal Sensitisation Thresholds using an expanded dataset and an *in silico* expert system, *Regul. Toxicol. Pharmacol.*, **2022**, 133, 104805.
6) https://www.ecetoc.org/publication/tr-087-contact-sensitisation-classification-according-to-potency/
7) https://echa.europa.eu/