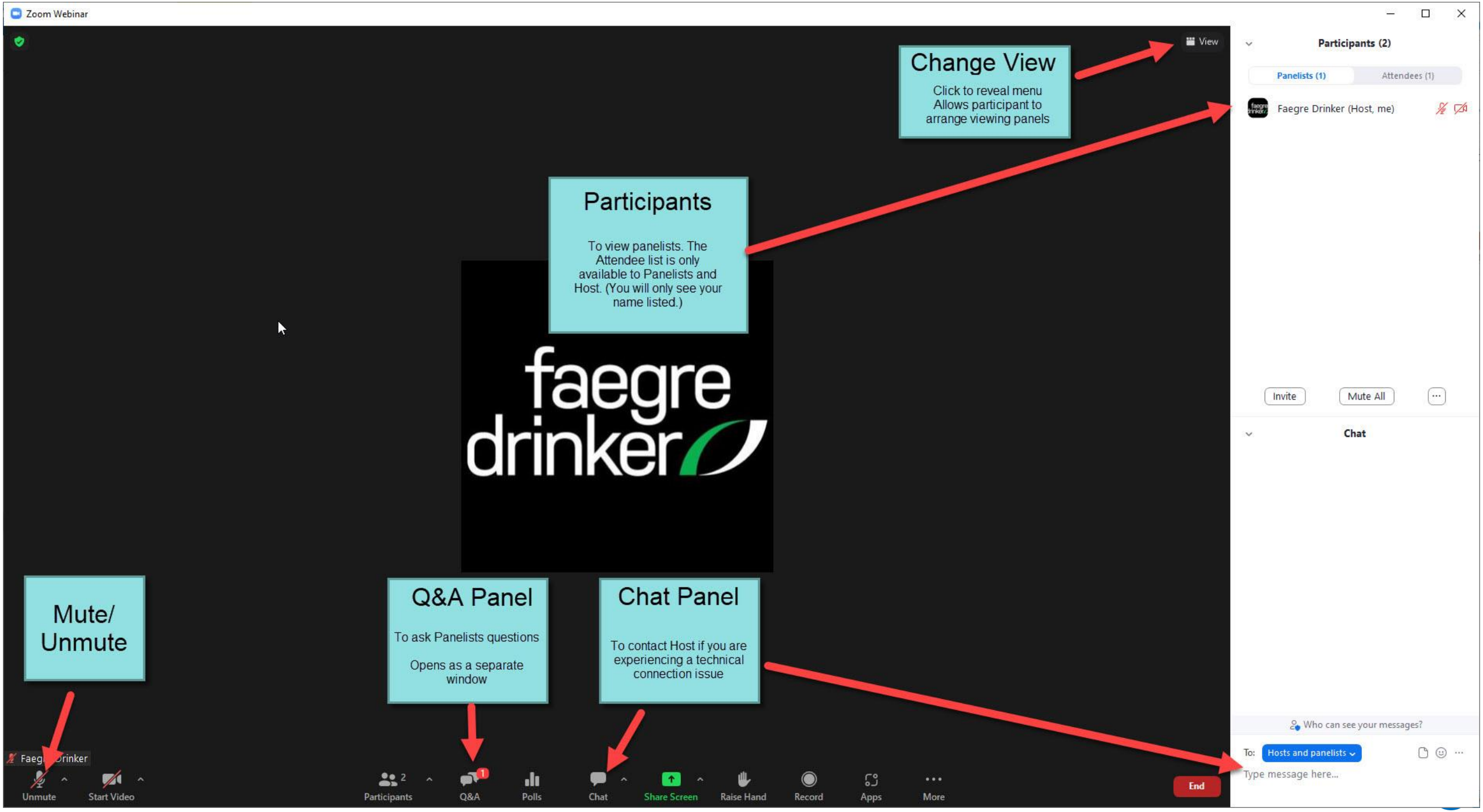
ELSIE Framework for Sensitization Assessment of E&Ls and Practical Application

September 22, 2022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Participants (2)
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To ask Panelists questions
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Chat
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Agenda


Introduction
Patricia Parris
Global Risk Assessment Services Toxicologist
Pfizer, Inc.
5

Introduction

Patricia Parris
Global Risk Assessment Services Toxicologist
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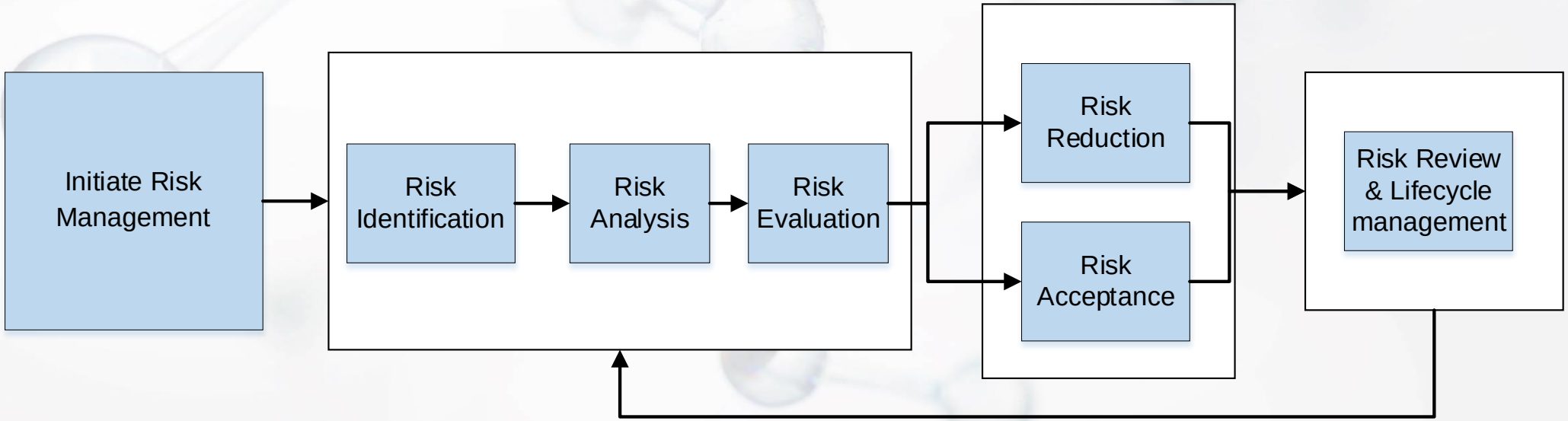
ELSIE Leachables Risk Management Approach

Identification of hazards and the analysis and evaluation of risks associated with probability of exposure to those hazards

Decision making to reduce and/or accept risks – reduce the risk to an acceptable level

Review and monitoring of risk management process outputs/results



Screening and Material Selection

Risk Assessment

Risk Control – Knowledge Gathering

Risk Control – Safety Assessment

Risk Review

www.elsiedata.org/elconcepts

Risk Control – Safety Assessment White Paper

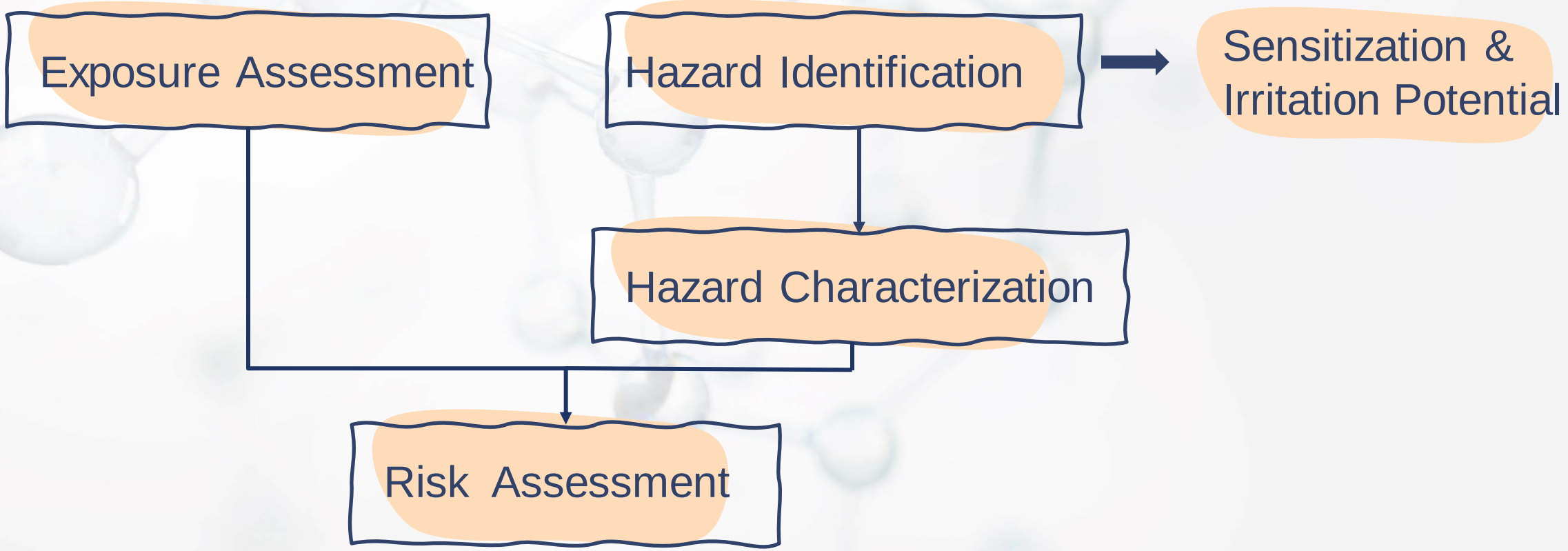
- Objective - Consolidate information related to toxicity of E&L and propose safety evaluation process flow based on understanding toxicities (including mutagenic potential)
  - Build on concepts in existing documents, e.g., ICH M7, ICH Q3A/B/C/D, PQRI, FDA
  - ELSIE publications Broschard et al 2016; Parris et al, 2020, Masuda-Herrara et al., 2022, Parris et al 2022

- Highlights areas where further harmonized guidance is needed:
  - **Default parenteral thresholds for compounds with limited toxicological data (Masuda-Herrara et al., 2022)**
  - **Evaluating endpoint-specific effects (e.g., irritation, sensitization Parris et al, 2022)**
- Application of M7 principles to E&L inconsistent
  - Route of administration and bioavailability considerations
  - (non-daily) dosing and less than lifetime (LTL) limits for non-mutagenic substances
- Risk assessment of polymers

ELSIE Sensitization Workstream

Geraldine Whelan
Title
GSK

Risk Assessment (e.g. of E&Ls)



Sensitization Assessment of E&Ls

- Sensitization potential of E&Ls is complex from both a biological and risk assessment perspective
  - Prevention of induction of sensitization
- Sensitization following dermal, respiratory and oral exposure has been studied, and provides potential approaches for drugs administered by these routes
  - Dermal Sensitization Thresholds and Quantitative Risk Assessment (QRA)
  - Lack of validated animal models and complex biology precluded development of predictive tools for respiratory and systemic sensitization
  - Local Lymph Node Assay (LLNA) – skin sensitizers (can detect respiratory sensitizers)
    - Activation of the immune system regardless of route of administration – surrogate for parenteral administration
- Further guidance needed on how to risk assess low level E&Ls with known or unknown sensitizing potential via parenteral routes of administration
  - ELSIE workstream set up to establish best practice

ELSIE Sensitization Workstream

Objectives:

1. Extract sensitization data from safety reports in ELSIE database
    - Relevant chemical space
2. Evaluate ELSIE sensitization potency with in silico tools
    - How many are skin sensitizers? How potent?
3. Scientific justification for threshold limits
    - Do the data support existing limits? Another approach?

Practical Application for Sensitization Assessment

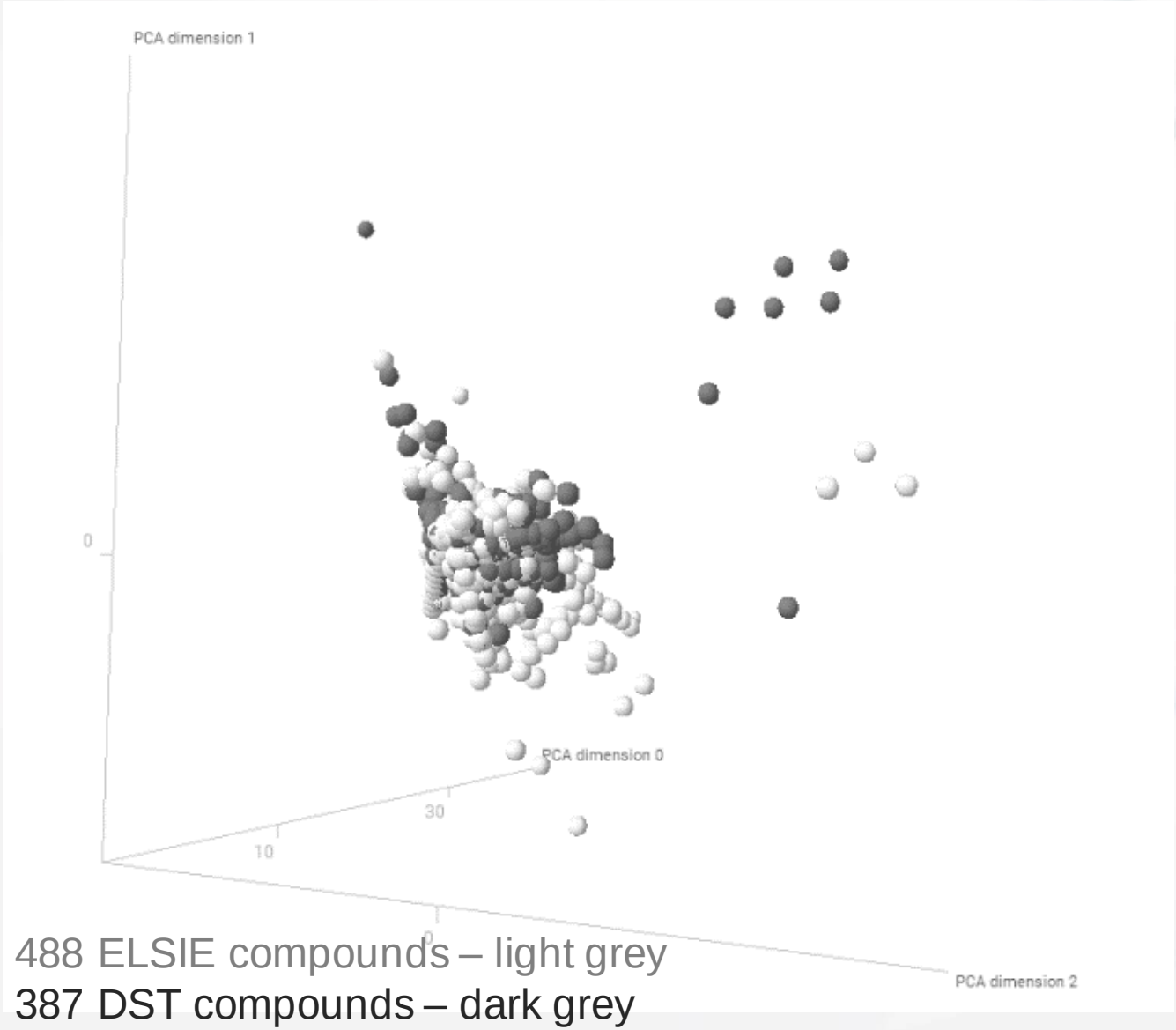
- 5 µg/day recommended qualification threshold for sensitization/irritation (PQRI, 2007 and 2021)
  - Conservative threshold
  - Derived based on 150 inhaled compounds primarily with regulatory agency chronic reference doses (RfDs) – sensitization endpoint not evaluated
  - Total inhaled dose assumed 100% deposition
  - Scientific basis of application to parenteral route not substantiated

- Challenges
  - Large volume parenterals
  - Lack of systemic sensitization data

- Considerations
  - Material characterization
  - In silico tools for prediction of sensitization potential
  - Incorporate skin sensitization potency into the assessment

Sensitization Assessment Framework: Science-driven risk-based approach to E&L sensitization assessment

Topical Products



488 ELSIE compounds – light grey
387 DST compounds – dark grey

- Good overlap between ELSIE and Dermal Sensitization Threshold (DST) compounds based on physicochemical properties:
  - Molecular weight
  - Lipophilicity
  - Polar surface area
- DST cluster contains neomycin – not relevant to E&Ls
- Use DST for sensitization assessment of E&Ls in topical drug products

E&L Sensitization Assessment in Inhalation or Parenteral Drug Products

1. In silico structural assessment and literature review for available data

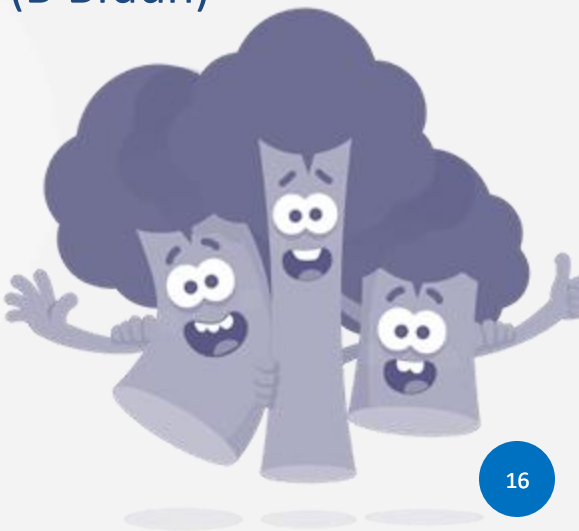
2. Presence of reactive domain and/or HPC
- Convert EC3% to a dose (µg/day) and conduct compound-specific MoE assessment

3. Weak, moderate or negligible risk of inducing sensitization -
Tox assessment based on other endpoints

Acknowledgements

ELSIE Workstream Members

- **Patricia Parris (Pfizer) Sensitization Co-Chair**
- **Geraldine Whelan (GSK) Sensitization Co-Chair**
- Shawn Bairstow (Baxter)
- Joel Bercu (Gilead)
- Uma Bruen (Organon)
- Anders Burild (Novo Nordisk)
- Courtney Callis (Eli Lilly)
- Jessica Graham (Genentech)
- Troy Griffin (Teva)
- Jedd Hillegass (Bristol Myers Squibb)
- Esther Johann (EMD Serono)
- Claire Kent (AstraZeneca)
- Agnes Koenig (B. Braun)
- Martin Kohan (AstraZeneca)
- Kim Li (Amgen)
- Elizabeth Martin (AstraZeneca)
- Alina Martirosyan (B Braun)
- Melisa Masuda-Herrera (Gilead)
- Constanca Porredon-Guarch (B Braun)
- Matthew Schmitz (Takeda)
- Brad Stanard (Ultragenyx)
- Eric Tien (Biogen)
- Jessica Whritenour (Pfizer)



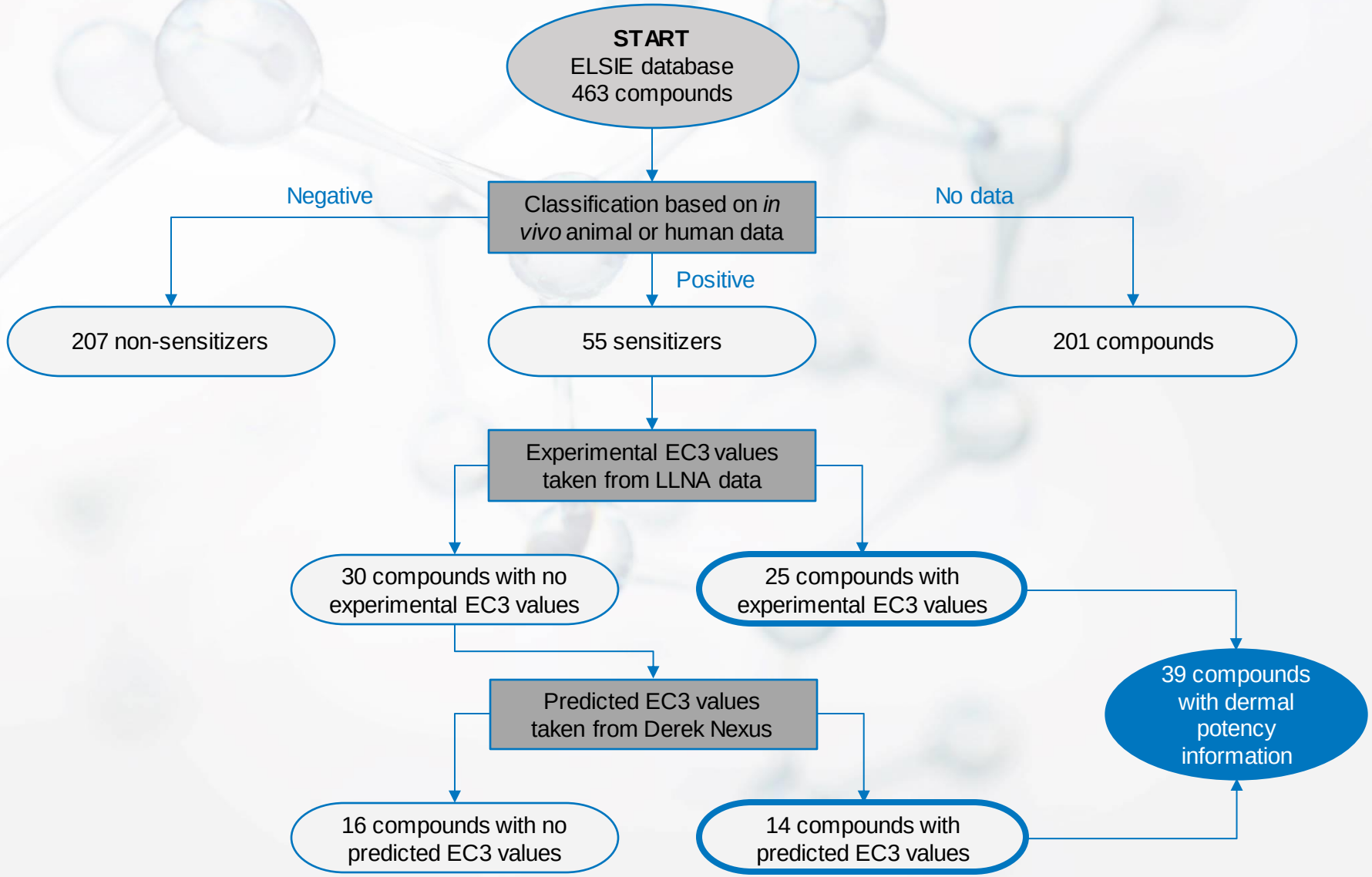
ELSIE Sensitization Data and Threshold Analysis

Martyn Chilton
Principal Scientist
Lhasa Limited

What do we know about the potency of E&Ls?

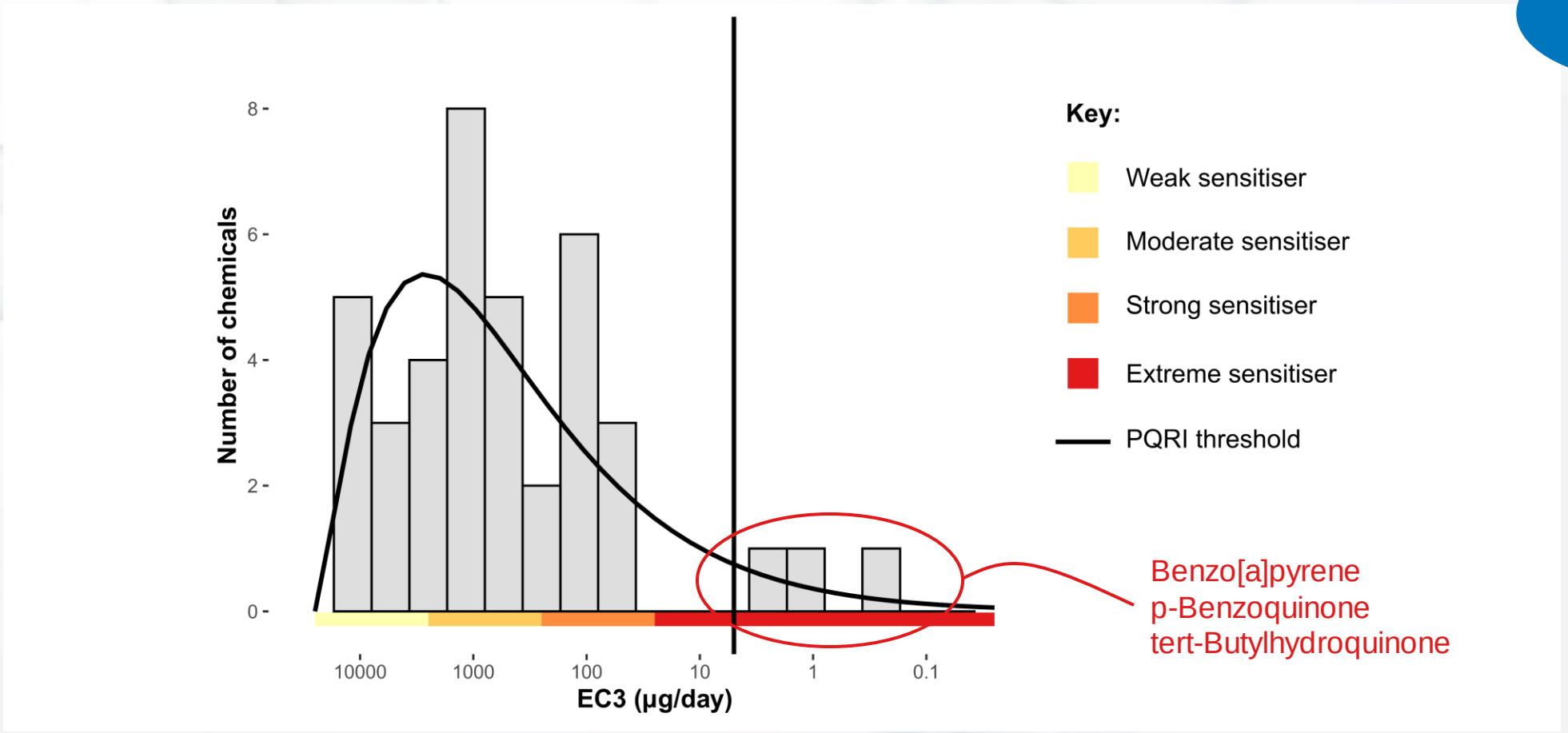
- Based on the chemicals in the ELSIE database:
  - 80% of E&Ls are non-sensitizers
  - 17% of E&Ls are weak/moderate sensitizers
  - 3% of E&Ls are strong/extreme sensitizers
- Various thresholds are used for E&Ls including:
  - ICH M7's mutagenic TTCs: 1.5, 10, 20 and 120 µg/day
  - ELSIE's non-mutagenic TTCs: 35, 110 and 180 µg/day
- How do these TTCs compare to the known potency of E&Ls?
  - Quantitative estimates of potency are required (i.e. EC3 values)

Collecting quantitative dermal potency data



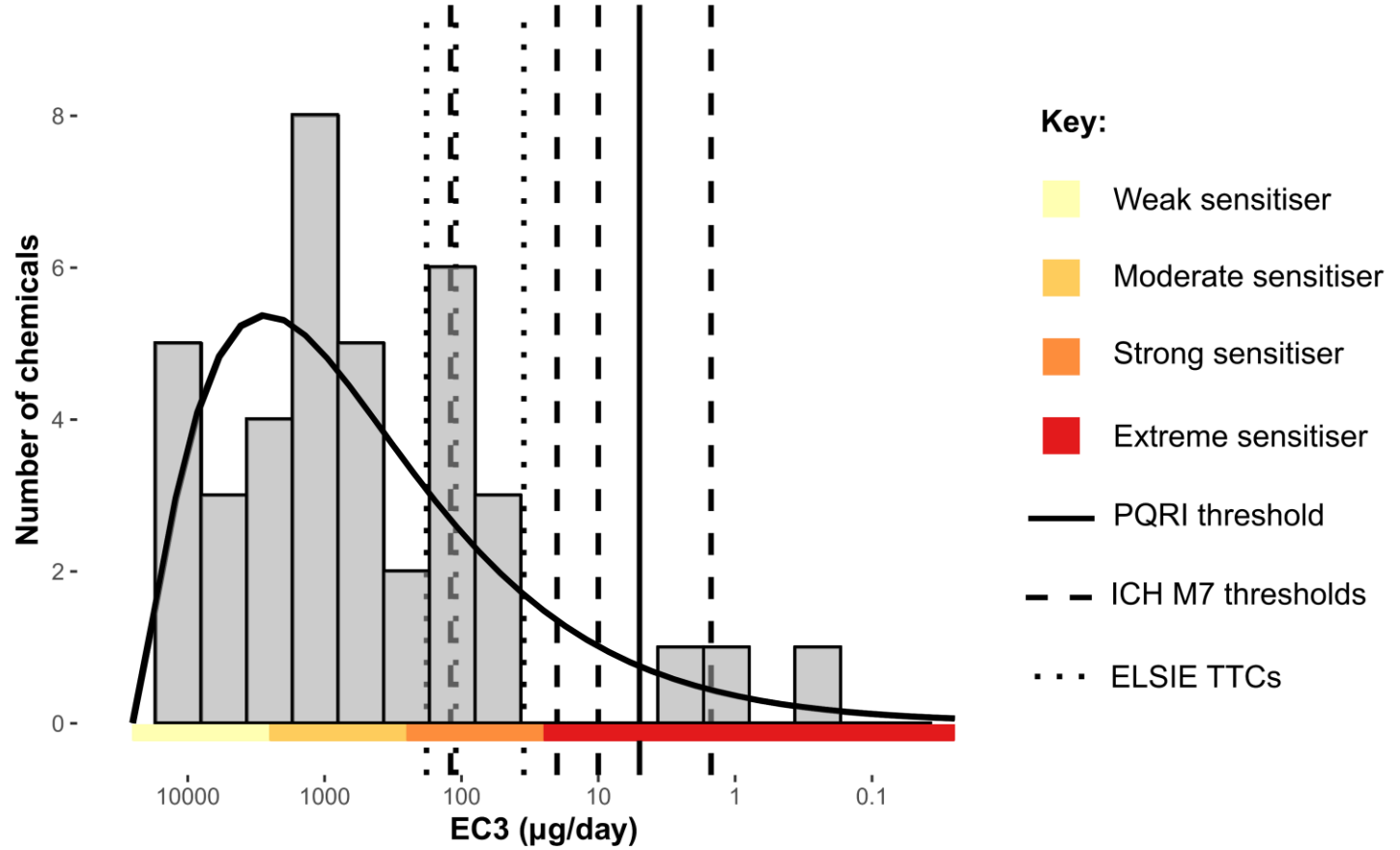
How potent are E&L sensitizers?

39 compounds with dermal potency information



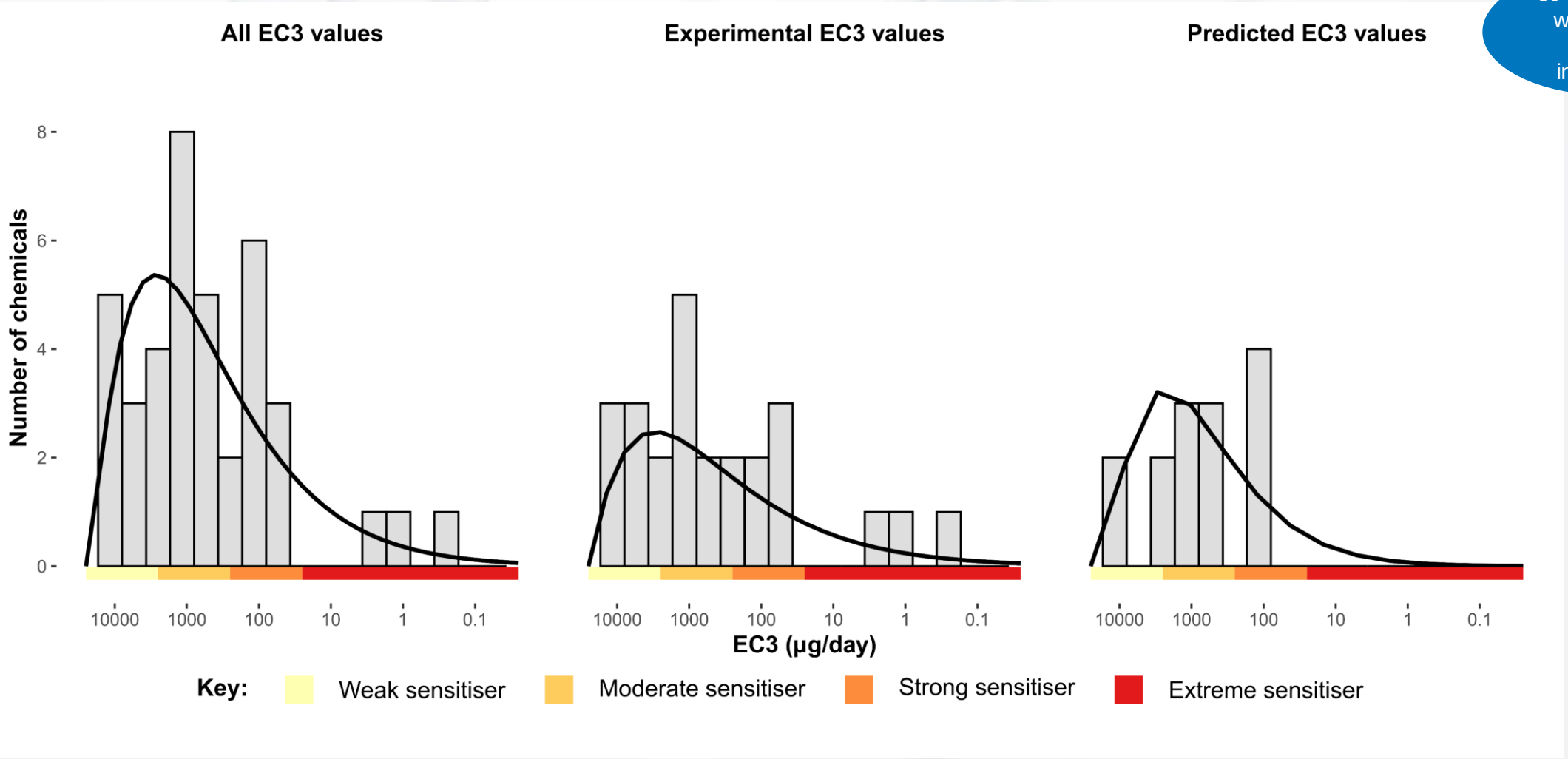
How do existing thresholds compare?

39 compounds with dermal potency information

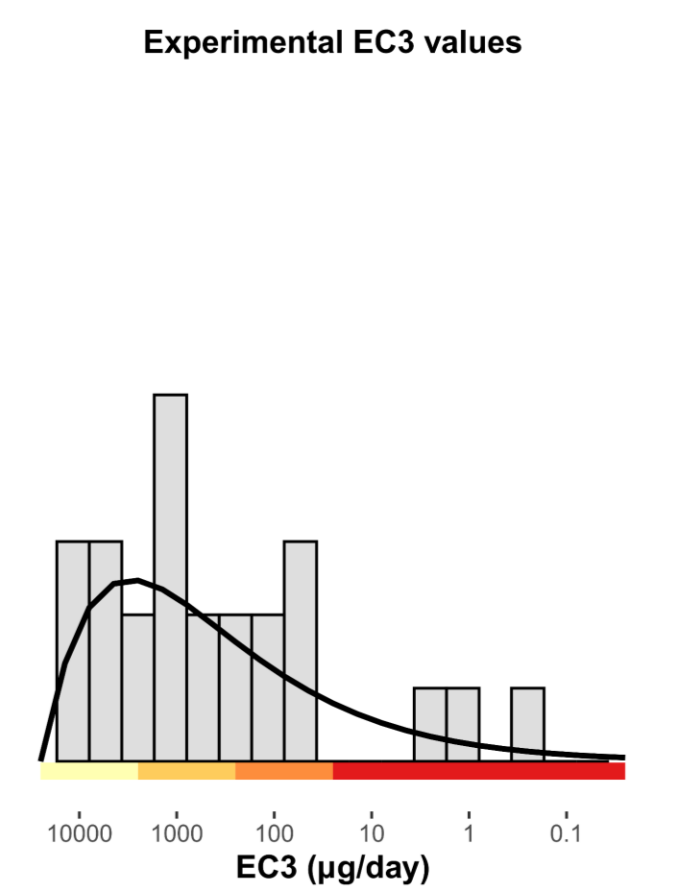


Are predicted EC3 values reliable?

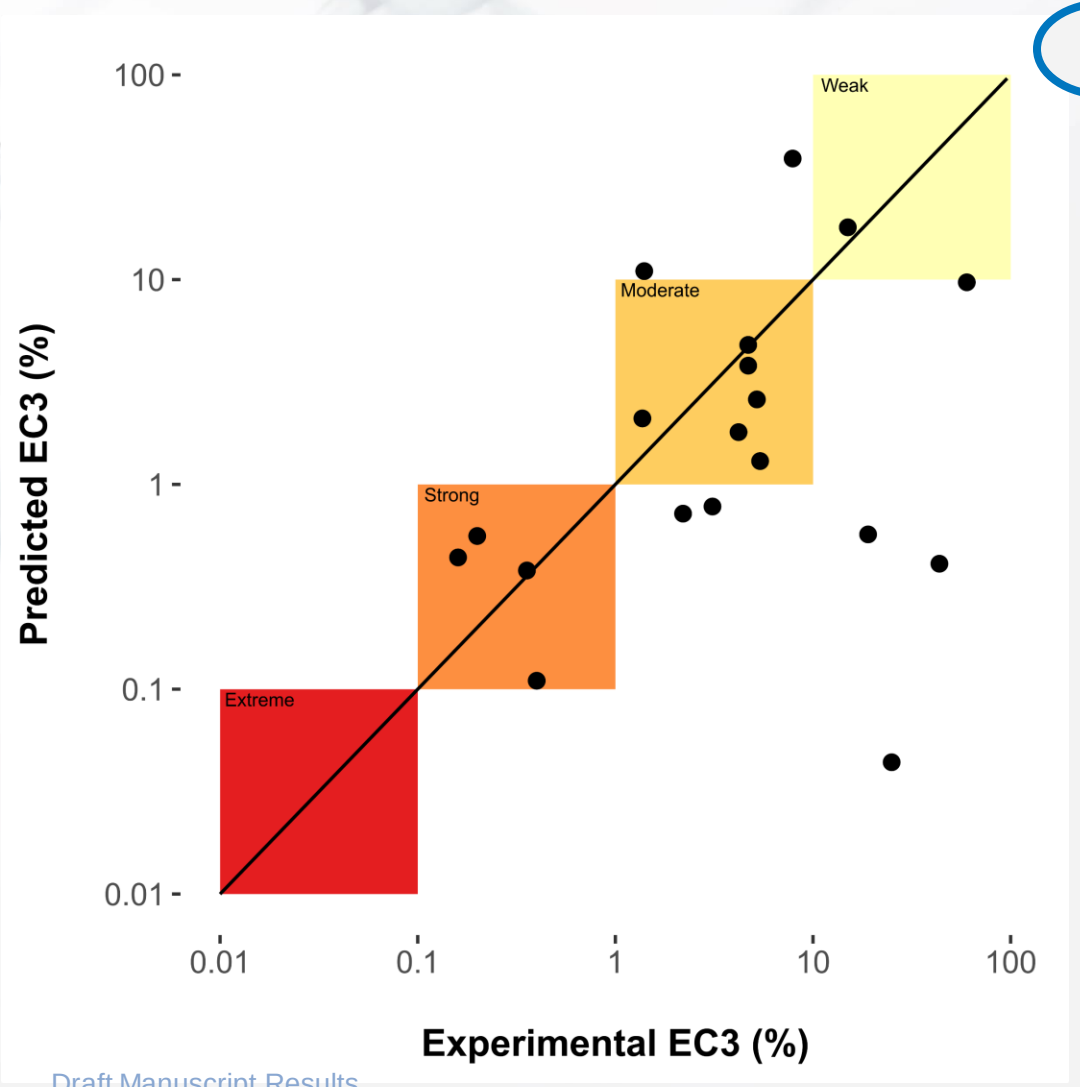
39 compounds with dermal potency information



Are predicted EC3 values reliable?



25 compounds with experimental EC3 values



Take home messages

- Sensitizing E&Ls are mostly weak/moderate
  - 69% of the dataset analysed has an EC3 value >1%
- Existing E&L thresholds are generally protective
  - 10 µg/day (ICH M7) would be protective 92% of the time
  - 35 µg/day (ELSIE TTC) would be protective 86% of the time
- For potential sensitizers, predicted EC3 values from Derek Nexus are conservative
  - 89% are in correct ECETOC potency category or more potent

Extended E&L Dataset Analysis

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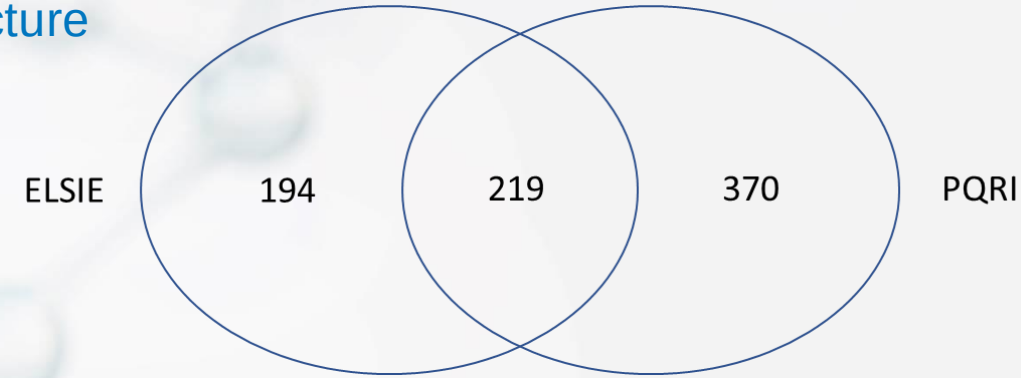
Vice President, Informatics
Instem

Objectives

- To create a representative database of E&L from the ELSIE and PQRI published datasets
- Understand common and unique chemicals and chemicals classes
- Identify chemical classes likely to flagged by *in silico* tools predicting
  - DNA-reactive mutagenicity
  - Dermal potent (strong or extreme) sensitization

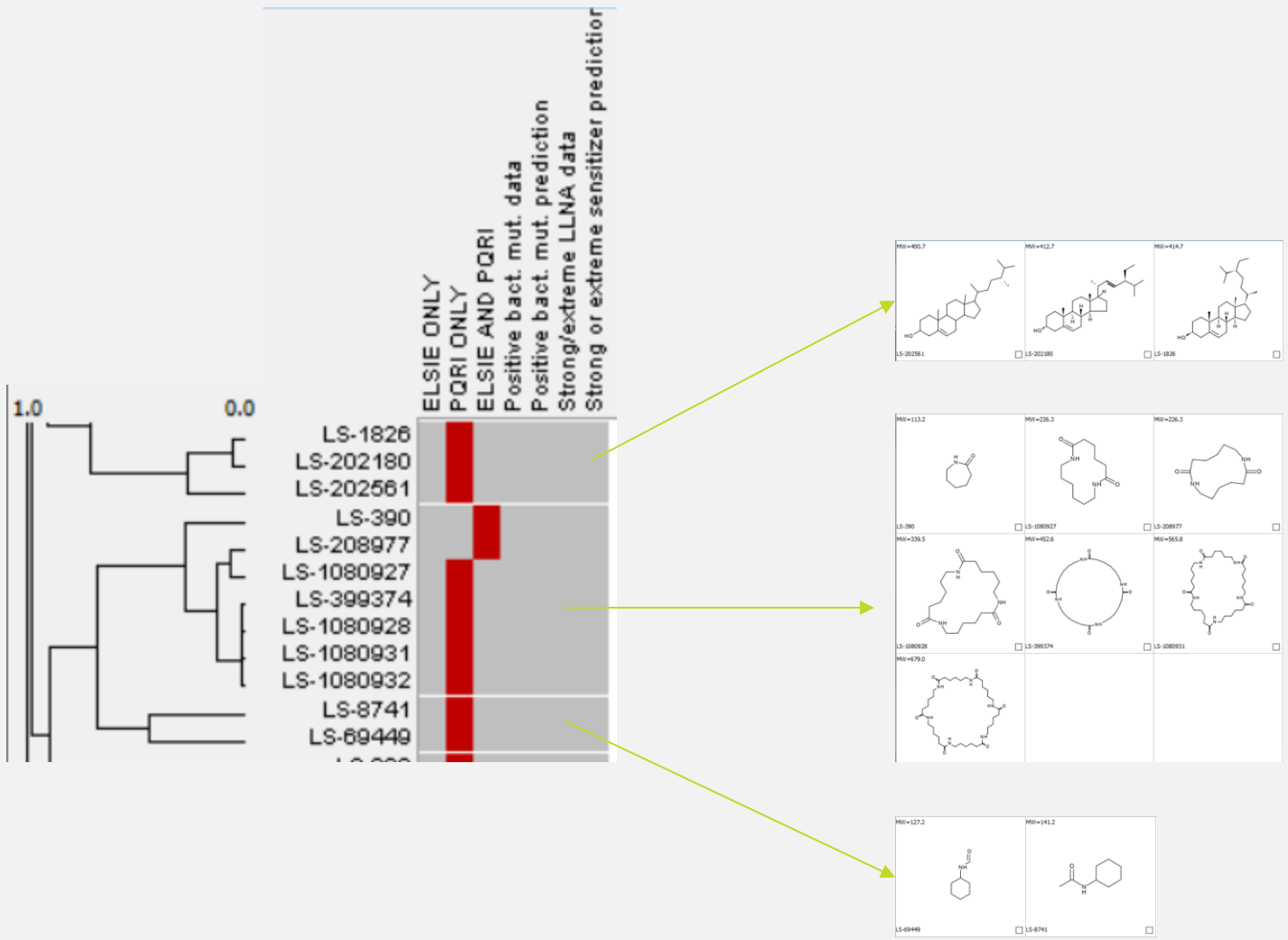
Combined ELSIE and PQRI datasets

- **Datasets:**
  - **ELSIE[1]**. 466 compounds compiled based on their being observed in pharmaceutical, biological and device applications and processes
  - **PQRI[2]**. 611 chemical structures includes compounds that have been known to extract or leach from manufacturing equipment and/or container closure components during the manufacture of parenteral drug products.
- **Processing**:
  - All chemicals in the datasets were mapped to a unique chemical after being converted to their structure-activity relationship (SAR) forms
    - salt forms are neutralized
    - complex structures, such as mixtures and polymers, are excluded from the set



1. Parris, et al., Sensitization Assessment of Extractables and Leachables in Pharmaceuticals: ELSIE Database Analysis (2022); elsiedatabase.org
2. PQRI 2021. Product Quality Research Institute PQRI, Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in 2. Parenteral Drug Products (Intravenous, Subcutaneous, and Intramuscular). October 2021

Identifying chemical classes through clustering

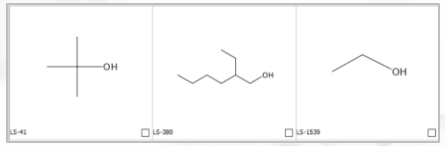


- 149 chemicals classes containing two or more chemicals
  - 5% (8/149) of classes contained only chemicals from the ELSIE dataset
  - 19% (29/149) of classes contain only chemicals from the PQRI dataset
  - 75% (112/149) of classes contained chemicals from both datasets

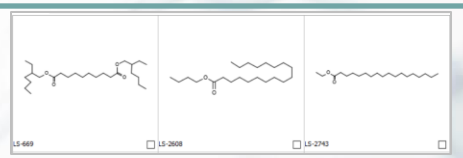
Chemical classes with 10 or more examples

Examples from the ELSIE and PQRI datasets

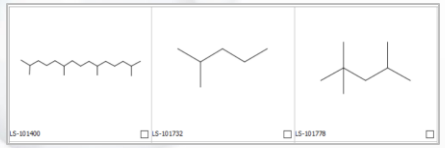
Alkyl cluster (acyclic, linear) (25)



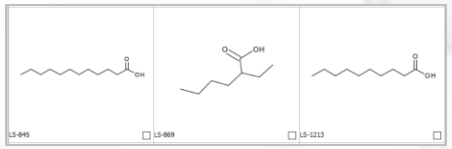
Alkyl alcohol analogs (19)



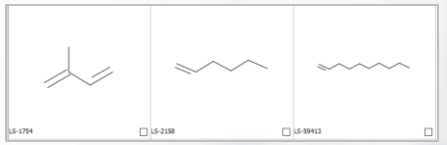
Di(2-ethylhexyl)sebacate analogs (21)



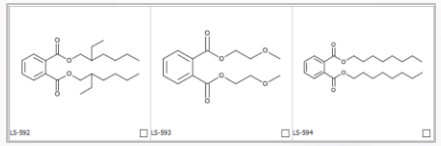
Alkyl cluster (acyclic, branched) (18)



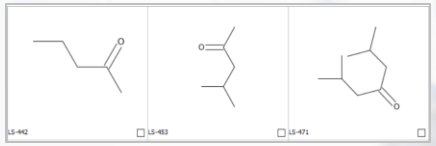
Butyric acid analogs (19)



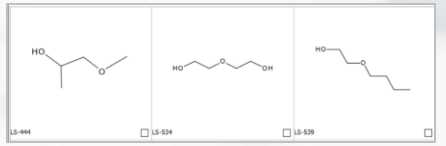
Propylene analogs (19)



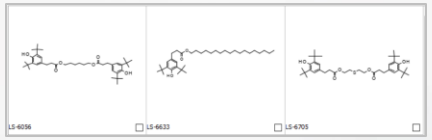
Dimethyl phthalate analogs (15)



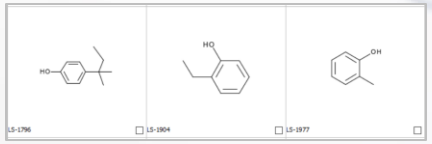
2-pentanone analogs (14)



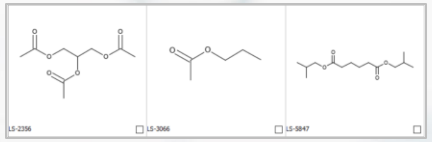
Butoxyethanol analogs (17)



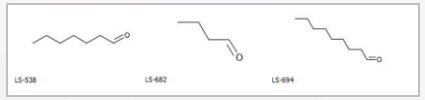
Methyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate analogs (13)



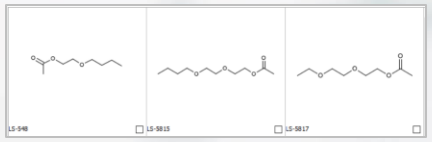
p-cresol analogs (10)



Ethyl acetate analogs (13)

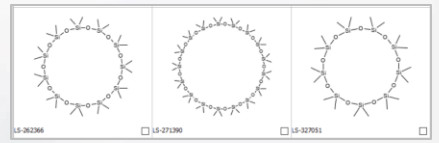


Butyraldehyde analogs (10)



2-Butoxyethanol acetate analogs (10)

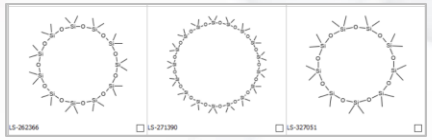
Examples from only ELSIE



Large cyclosiloxanes (12)

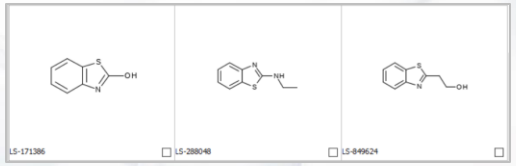
Unique chemical classes to ELSIE and PQRI with >3 structures

Examples from only ELSIE

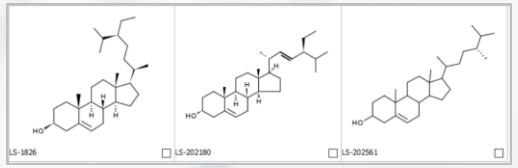


Large cyclosiloxanes (12)

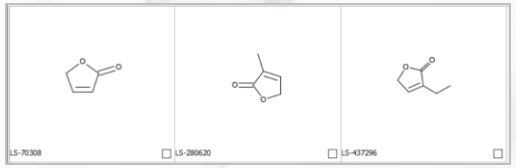
Examples from only PQRI



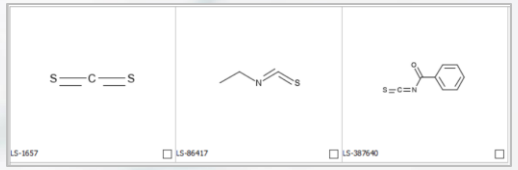
Substituted 1,3-benzothiazole



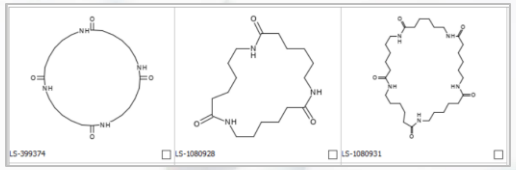
Beta-Sitosterol analogs (3)



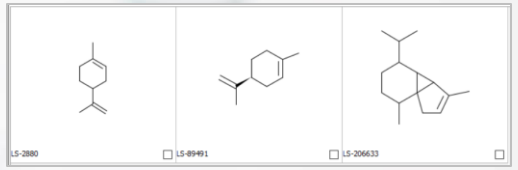
Butenolide analogs (4)



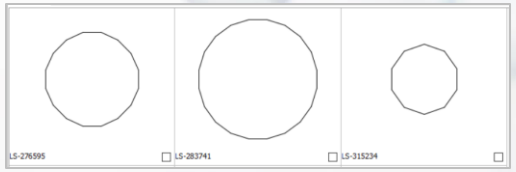
Isothiocyanate analogs (3)



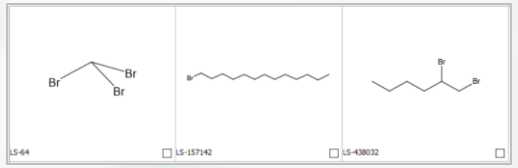
Amino(NH)carbonyl, N-(alkyl, cyc)- (4)



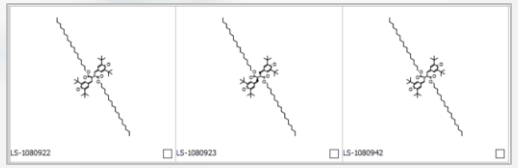
dl-limonene analogs (3)



Alkyl cluster (cyclic) (4)



Bromide, alkyl (3)



Unconjugated Bisquinonemethide analogs (3)

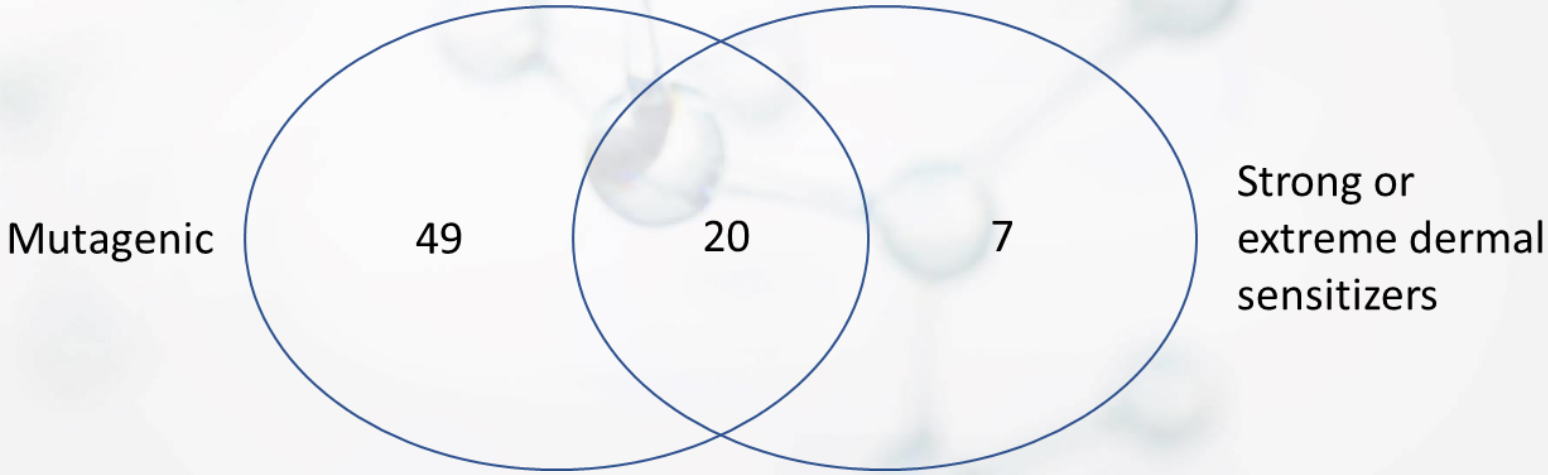
In silico predictions

- Experimental data identified for the combined dataset
  - Bacterial mutagenicity experimental data[1]
  - Dermal sensitization ECETOC potency categories (strong or extreme)[2]
- *In silico* model based on two methodologies were used in the absence of experimental data
  - DNA-reactive mutagenicity[3]
  - Potent dermal sensitizers (strong or extreme)[4]
- Expert review
  - Consensus overall calls based on an expert review following standard documented procedures[5]
  - This review consisted of an interrogation of model features, an assessment of structurally similar analogs, and a review of reaction mechanisms.

1. Leadscope bacterial mutagenicity reference database that includes ~22,000 chemicals
2. Leadscope LLNA reference databases that includes ~1,500 chemicals
3. Leadscope Bacterial Mutation expert alerts v8 and Leadscope Bacterial Mutation statistical-based QSAR model v2
4. Leadscope LLNA statistical version (v3) and LLNA alerts version (v2)
5. Myatt GJ, et al., (2018) In silico toxicology protocols. Regul Toxicol Pharmacol 96:1–17

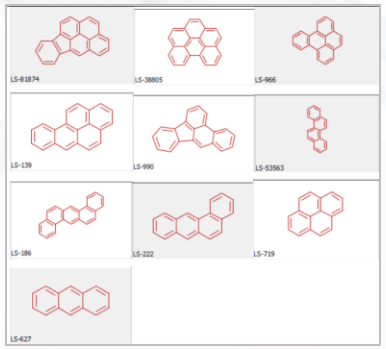
Prevalence of mutagens and potent sensitizers in combined dataset

- 9% (69/783) of chemicals were flagged as potential mutagens
- ~4%(27/783) were flagged as potent dermal sensitizers
- For chemicals predicted to the potent sensitizers, 74% (20/27) are also predicted to be mutagens

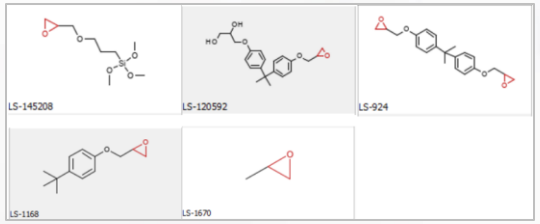


Main alerts fired for bacterial mutagenicity and potent sensitization

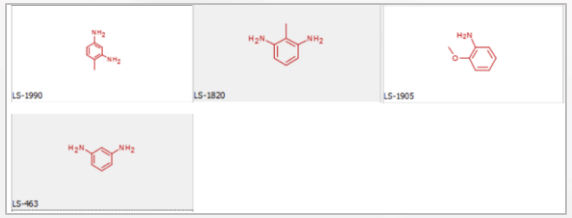
Bacterial mutagenicity alerts



47: polycyclic aromatic hydrocarbons (10)

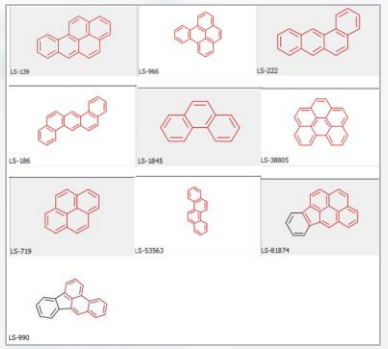


159: unhindered epoxide (5)

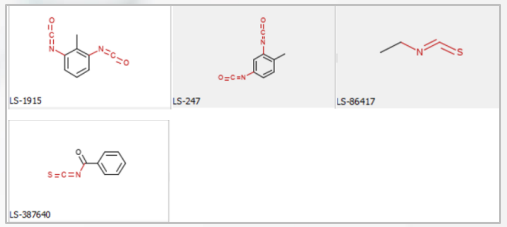


267: aromatic amine(NH2) (strong activating anilines) (4)

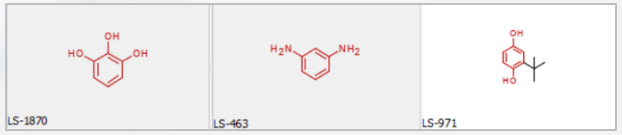
Potent sensitization alerts



53: Polyaromatic hydrocarbon (3)



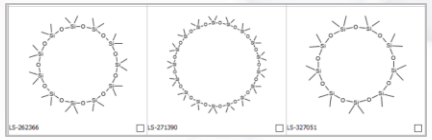
32: Alert:Iso(thio)cyanates (4)



13: Aromatic diamino-, dihydroxy-, or amino-hydroxy- compounds (3)

Prediction of DNA-reactive mutagenicity and potent sensitization for unique chemical classes

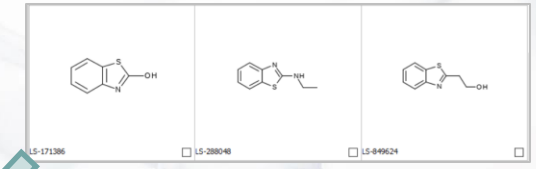
Examples from only ELSIE



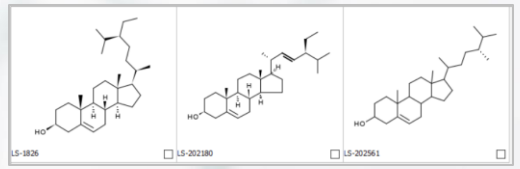
Large cyclosiloxanes (12)

1 flagged as mutagen, unrelated to the chemical class

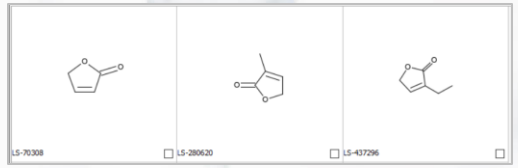
Examples from only PQRI



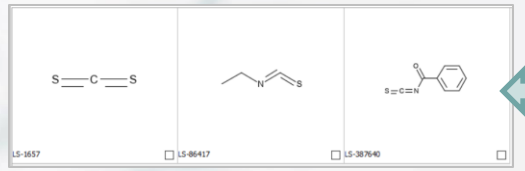
Substituted 1,3-benzothiazole



Beta-Sitosterol analogs (3)

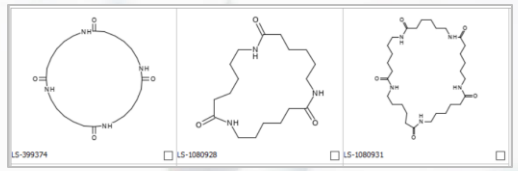


Butenolide analogs (4)

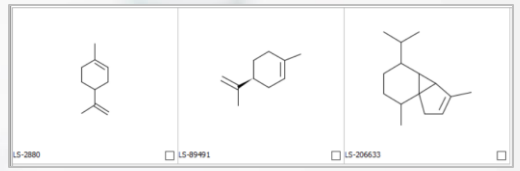


Isothiocyanate analogs (3)

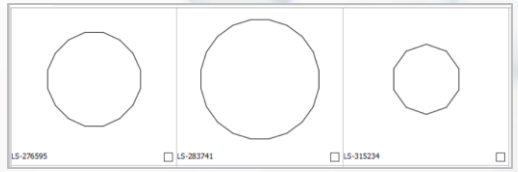
1 flagged as a potential mutagen, 2 flagged as potential potent dermal sensitizer



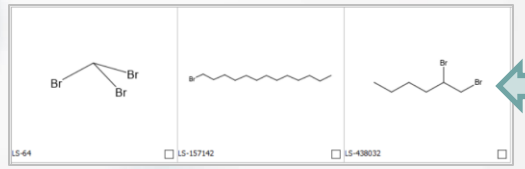
Amino(NH)carbonyl, N-(alkyl, cyc)- (4)



dl-limonene analogs (3)

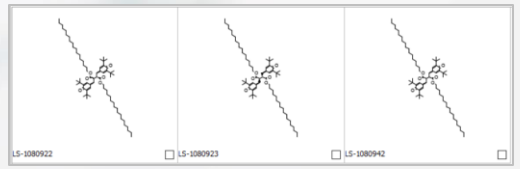


Alkyl cluster (cyclic) (4)



Bromide, alkyl (3)

2 out of the 3 chemicals were flagged as potential mutagens; however, acceptable limits may be derived for this class



Unconjugated Bisquinonemethide analogs (3)

Conclusions

- Combining ELSIE and PQRI dataset created a large and representative dataset of 783 E&Ls
  - 219 chemicals in both ELSIE and PQRI datasets
  - 75% of the chemical classes included examples from both the ELSIE and PQRI
  - Unique classes included:
    - Large cyclosiloxanes (only in the ELSIE dataset)
    - Isothiocyanates (only in the PQRI dataset)
- *In silico* analysis
  - 9% (69/783) of chemicals were flagged as potential mutagens
  - ~4% (27/783) were flagged as potent dermal sensitizers
    - 74% (20/27) potent dermal sensitizer predicted as mutagens
      - 7 predicted potent dermal sensitizers not predicted as mutagens
  - Only two classes (≥3 examples) unique to PQRI had multiple chemicals that flagged for mutagenicity and/or potent dermal sensitization
  - Analysis supports Parris et al., 2022 finding of low prevalence for potent dermal sensitizers in the E&L chemical space

Parris et al., Sensitization Assessment of Extractables and Leachables in Pharmaceuticals: ELSIE Database Analysis (2022

Panel Discussion

Panel Discussion

Moderator

Jessica Whritenour

Regulatory Toxicology Lead
Drug Safety Research and Development
Pfizer, Inc.

Geraldine Whelan

GSK

Martyn Chilton

Principal Scientist
Lhasa Limited

Patricia Parris

Global Risk Assessment Services Toxicologist
Pfizer, Inc.

Bruce Naumann

Retired Merck/MSD

Glenn J. Myatt

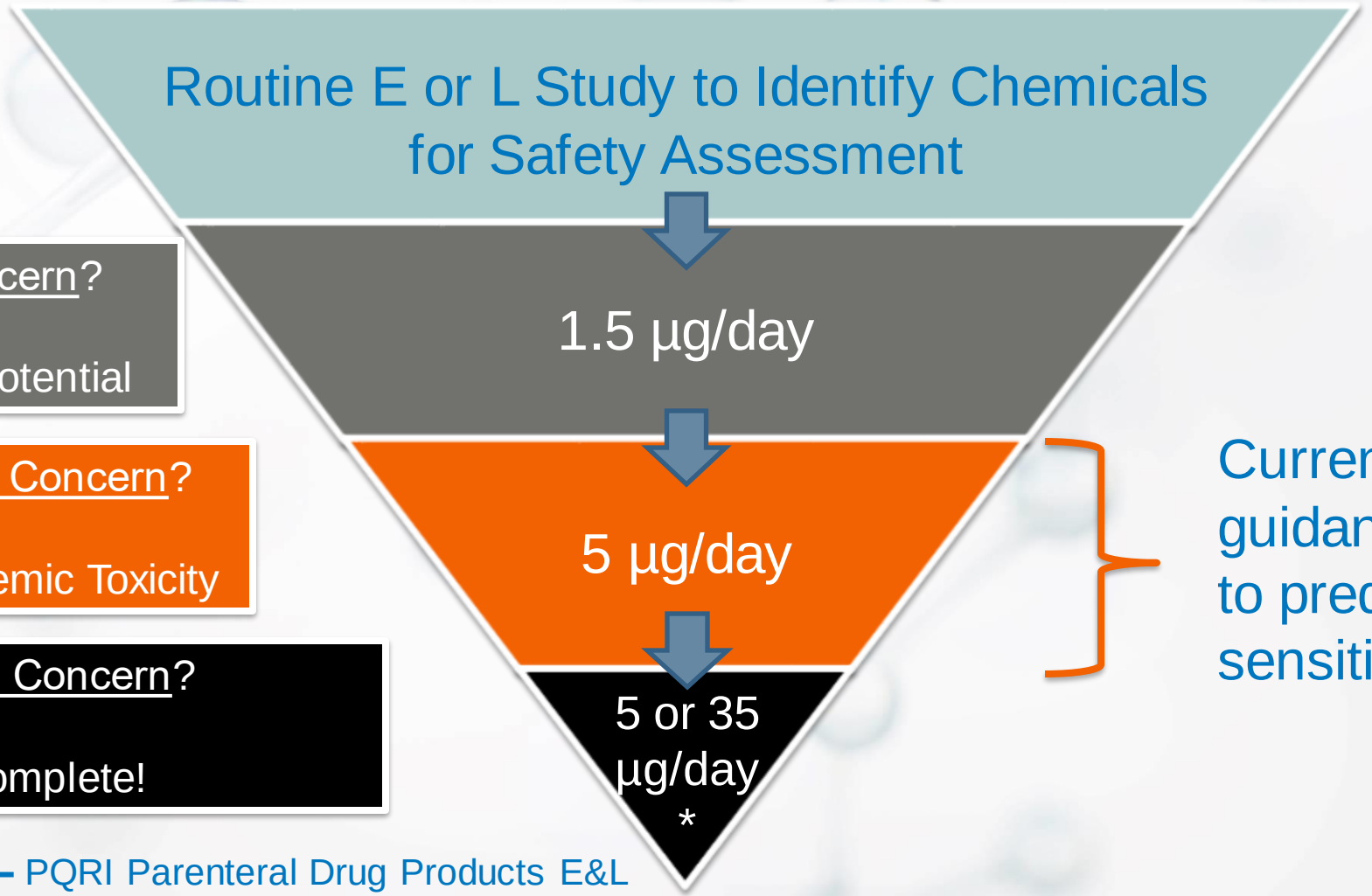
Vice President, Informatics
Instem


ELSIE
Extractables and Leachables Safety Information Exchange

Thank you!!

Back-Up Slides

PQRI Threshold Approach



≥1.5 Genotoxic Concern?
Yes – Qualify
No – Consider S/I Potential

≥5 Sensitizer/Irritant Concern?
Yes – Qualify
No – Consider Systemic Toxicity

≥5 Systemic Toxicity Concern?
Yes – Qualify
No –Qualification Complete!

Currently no guidance or models to predict systemic sensitization

***Recent publications –** PQRI Parenteral Drug Products E&L Recommendations, PDA, Oct 2021

Masuda-Herrera et al., (2022) ELSIE Parenteral E&L TTCs, PDA, Jan 2022