THE THRESHOLD APPROACH

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES
BASEL
27-28 FEBRUARY, 2020

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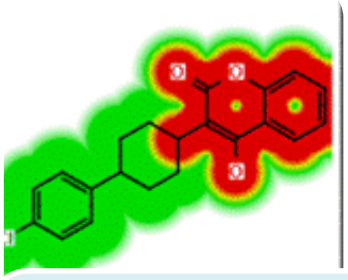
Bridging E&L- basic concept

EXTRACTABLES

Identification

- Knowledge of material
- What **CAN** come out



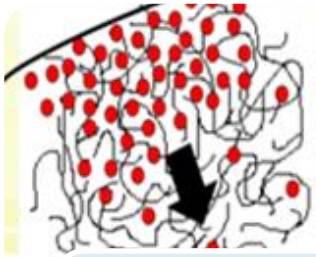
Initial Toxicological Evaluation

Example:

Cramer + Derek Nexus

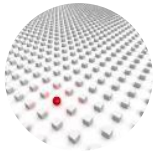
Toxicologist/ consultant

Select Targets



LEACHABLES

- What **DOES** come out in the drug product

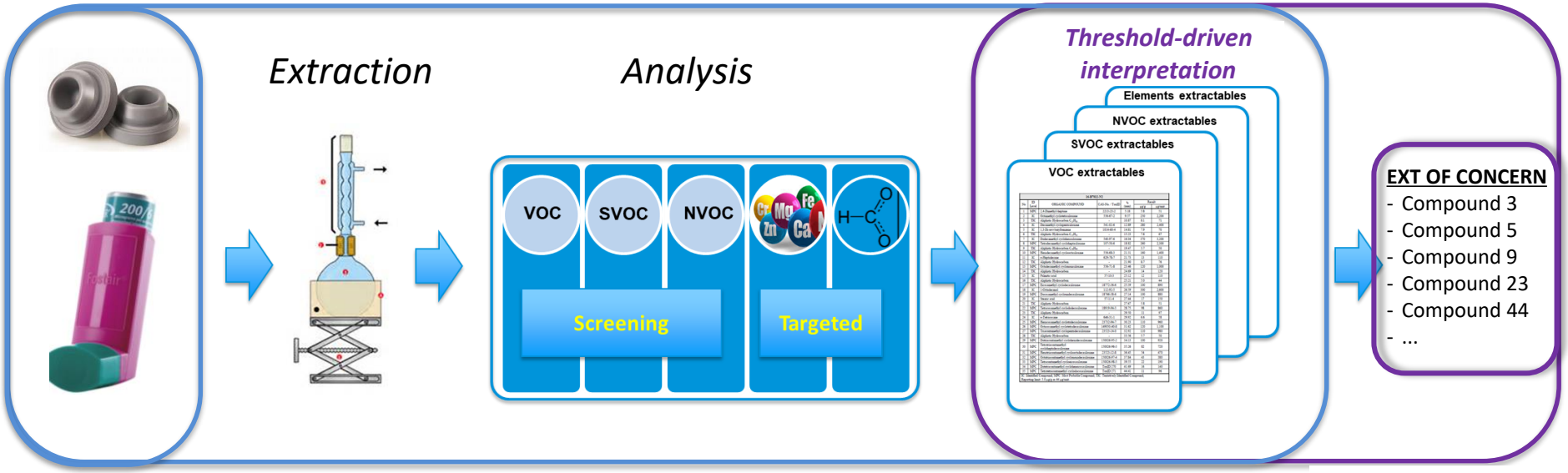


Screening

Target

Bridging E&L- basic concept

TYPICAL EXTRACTABLES STUDY



Packaging (test material)

Comprehensive EXT data set

Target compounds for LEA study

Applying threshold approach filters out "Extractables of Concern"

- Safety evaluation on results of an extractables study
- Critical information for leachables study

The threshold approach – organic compounds

SAFETY CONCERN THRESHOLD (SCT)

*"Threshold below which a leachable would have a dose so low as to present negligible **safety** concerns from carcinogenic and non-carcinogenic toxic effects"*

PQRI (Product Quality Research Institute)

- Chronic therapy
- Threshold approach dependent on the **administration route** of the final product:
  - OINDPs (Orally Inhaled and Nasal Drug Products)
  - PDPs: Parenteral Drug Products
  - ODPs: Ophthalmic Drug Products
  - Oral and Topical/Transdermal products

Bridging E&L- overview

1. Bridging Extractables and Leachables - basic concept
2. **The Threshold approach**
    2.1 Organic compounds
        - Safety Concern Theshold (SCT)
        - Threshold of Toxicological Concern (TTC)
    2.2 Elements
        - Permitted Daily Exposure (PDE)
    2.3 Analytical Evaluation Threshold (AET)
3. FIT screening evaluation (v2.0)
    - Subdivision of identified compounds into classes?
    - Derek assessment: rule based SAR assessment
4. Summary

2.1 The threshold approach – organic compounds

SAFETY CONCERN THRESHOLD (SCT)

Orally Inhaled and Nasal Drug Products (OINDPs):

- **PQRI "Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled Drug Products" (SEP 2006).**

Compound class details	Suggested threshold level
Qualification Threshold (QT): Threshold below which a given leachable is not considered for safety qualification unless the leachable presents structure-activity relationship (SAR) concerns	5 µg/day
Safety Concern Threshold (SCT): Threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and noncarcinogenic toxic effects	0.15 µg/day

2.1 The threshold approach – organic compounds

SAFETY CONCERN THRESHOLD (SCT)

Parenteral Drug Products (PDPs): ***(to be published)***

- **Presentation Dennis Jenke " The PODP Best Demonstrated Practice Recommendations – Chemistry and Toxicology, April 2016, Venice, PDA-Europe Extractables and Leachables Workshop."**

Tox endpoint	General tox.	Sensitizer & irritant	Carcinogen
Class	Class I	Class II	Class III
Threshold level (µg/day)	50	5	1.5 (PDP-SCT)

2.1 The threshold approach – organic compounds

Ophthalmic Drug Products (ODPs): ***(to be published)***

Thresholds are concentration-based, not dose-based

For confirmed leachables:

- Above 1 ppm –report
- 10 ppm – identification (in practice most companies ID at 1 ppm)
- 20 ppm – qualify

Oral and Topical/transdermal products:

no threshold level available yet

2.1 The threshold approach – organic compounds

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC)

"Threshold of Toxicological Concern (TTC) concept was developed to define an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects"

ICH M7 guideline

- TTC in function of therapy duration
- Limited to the evaluation of **mutagenic impurities**
- Additional cancer risk of 1 in 100.000 over life-time exposure

Duration of treatment	≤ 1 month	> 1-12 months	> 1-10 years	> 10 years
Daily intake (µg/day)	120	20	10	1.5

2.1 The threshold approach – organic compounds

Tox Endpoint	Others	Sensitizer & Irritant	Carcinogen
Class	Class I	Class II	Class III
Threshold Level (µg/day)	50	5	1.5
<10 years	**50**	**5**	10

However….

- The staged approach of ICH M7 only applies for **mutagenic impurities**
- No staged approach can be applied for irritants and sensitizers, since they have an immediate effect

Thus…

- All compounds exceeding 5 µg/day should be evaluated for irritation/sensitization

2.2 The threshold approach – Elements

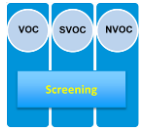
PERMITTED DAILY EXPOSURE (PDE)

ICH Q3D guideline

- Lists PDE in function of administration route
- Limited list of elements (e.g. typical glass elements or rubber elements are no included)

Element	Class[2]	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

ANALYTICAL EVALUATION THRESHOLD (AET)



➔ **Translating the SCT into Analytical Thresholds for Extractables studies**

$$\text{AET}\left(\frac{\mu g}{test\ item}\right) = \frac{\text{SCT}\left(\frac{\mu g}{\text{day}}\right)}{\text{number of doses/day}} \text{ x } \frac{\text{number of doses}}{\text{test item}}$$

➔ **Screening methods are semi-quantitative: correction factor of 50%**

$$\text{Final AET} = \frac{\text{AET}}{2}$$

Cornerstone of all E&L testing:

Compounds detected below the (Final) AET are considered to be toxicologically safe and should not be considered for toxicological assessment

2.3 The threshold approach – AET

Calculation AET – example 1 (small volume parenteral)

- Vial with rubber stopper
- Filling volume : 1 mL
- Maximum daily intake: 1 vial/day or 1 mL/day
- Final AET based on SCT for PDPs?

$$\text{AET} = \frac{\text{threshold}}{dose/day} \text{ x } \frac{total\ \#\ doses}{test\ item}$$

$$= \frac{1.5\ \mu g/day}{1\ dose/day} \text{ x } \frac{1\ dose}{test\ item}$$

$$= 1.5\ \mu\text{g/test item}$$

$$\text{Final AET} = \frac{1.5\ \frac{\mu g}{test\ item}}{2} = 0.75\ \mu\text{g/test item}$$

50% uncertainty for screening methods

2.3 The threshold approach – AET

Calculation AET – example 2 (filter for PDP)

- Filter is used to produce 1000 doses for parenteral application
- Maximum daily intake: 1 dose/day
- Final AET based on SCT for PDPs?

$$\text{AET} = \frac{\text{threshold}}{dose/day} \times \frac{total\ \#\ doses}{\#\ filters}$$

$$= \frac{1.5\ \mu g/day}{1\ dose/day} \times \frac{1000\ doses}{filter}$$

$$= 1500\ \mu g/\text{filter}$$

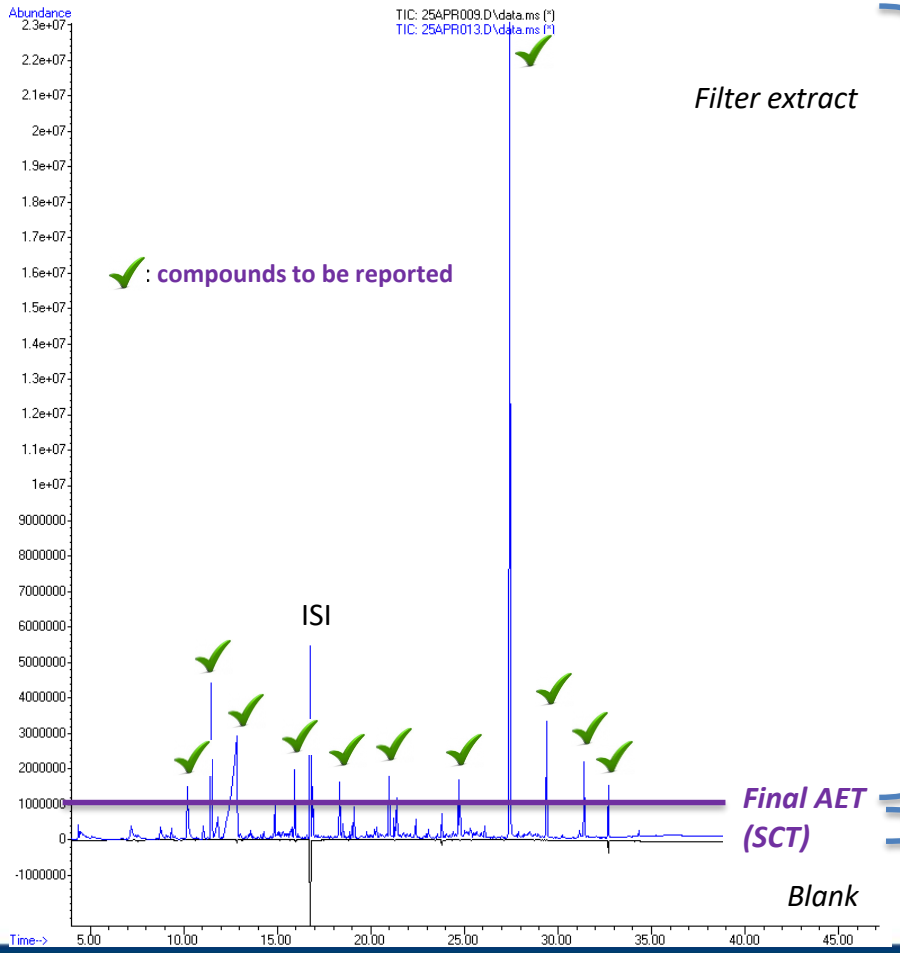
$$\text{Final AET} = \frac{1500\ \mu g/\text{filter}}{2} = 750\ \mu g/\text{filter}$$

50% uncertainty for screening methods

2.3 The threshold approach – AET (organic compounds)

➔ Final AET based on SCT is often used as Reporting Limit in extractables studies

Example 2: filter



Reported compounds

	Result (µg/filter)
COMPOUND #1	100
COMPOUND #2	200
COMPOUND #3	1300
COMPOUND #4	2000
COMPOUND #5	400
COMPOUND #6	250
COMPOUND #7	13000
COMPOUND #8	100
COMPOUND #9	47000
COMPOUND #10	400
COMPOUND #11	100
COMPOUND #12	5500
COMPOUND #13	33000
COMPOUND #14	1200
COMPOUND #15	3500

Compounds not considered for toxicological evaluation

Bridging E&L- overview

1. Bridging Extractables and Leachables - basic concept

2. The Threshold approach

    2.1 Organic compounds

        - Safety Concern Theshold (SCT)

        - Threshold of Toxicological Concern (TTC)

    2.2 Elements

        - Permitted Daily Exposure (PDE)

    2.3 Analytical Evaluation Threshold (AET)

3. FIT screening evaluation (v2.0)

    - Subdivision of identified compounds into classes?

    - Derek assessment: rule based SAR assessment

4. Summary

3. FIT screening evaluation (v2.0)

- How to determine (potential) toxicological endpoints of an organic compound?

- literature data often very limited or non existent:
  - *polymer oligomers*
  - *polymer degradation compounds*
  - *polymer additive degradation compounds*
  - *reaction products*

- (Q)SAR ((Quantitative) Structure Activity Relationship) software packages might assist in assessing the safety risk of
  - Rule-based SAR
    E.g. Derek Nexus
  - Statistically-based SAR
  - E.g. Sarah Nexus, MultiCase, Leadscope

Fast Initial Toxicity (FIT) Screening (PQRI classes)

3. FIT screening evaluation (v2.0)

FIT screening evaluation?

Derek Nexus software (Lhasa Ltd):

- Compounds submitted to a rule based Structure Activity Relationship (SAR) assessment
- Several 'toxicological end points', 'likelyhood levels' and 'negative predictions' are used

Endpoints included		
Carcinogenicity	Cerebral oedema	Respiratory sensitization
Photocarcinogenicity	Chloracne	Occupational asthma
Chromosome damage *in vitro*	Cumulative effect on white cell count and immunology	Skin sensitization
Chromosome damage *in vivo*	Cyanide-type effects	photoallergenicity
photo-induced chromosome damage *in vitro*	High acute toxicity	Thyroid toxicity
Genotoxicity *in vitro*	Methaemoglobinaemia	Rapid prototype: bradycardia
Genotoxicity *in vivo*	Neurotoxicity	Rapid prototype: nephrotoxicity
Photogenotoxicity *in vitro*	Ocular toxicity	Rapid prototype: hepatoxicity
Photogenotoxicity *in vivo*	Oestrogenicity	Rapid prototype: kidney disorders
Hepatotoxicity	Peroxisome proliferation	Rapid prototype: mitochondrial dysfunction
hERG channel inhibition *in vitro*	Phospholipidosis	Rapid prototype: bladder disorders
Irritation (of the eye)	Phototoxicity	Rapid prototype: blood in urine
Irritation (of the gastrointestinal tract)	Pulmonary toxicity	Rapid prototype: thyroid toxicity
Irritation (of the respiratory tract)	Nephrotoxicity	Rapid prototype: splenotoxicity
Irritation (of the skin)	Uncoupler of oxidative phosphorylation	Rapid prototype: bone marrow toxicity
Lachrymation	Mutagenicity *in vitro*	Rapid prototype: adrenal gland toxicity
Alpha-2-mu-Globulin nephropathy	Mutagenicity *in vivo*	Rapid prototype: cardiotoxicity
Anaphylaxis	Photomutagenicity	Rapid prototype: chromosome damage *in vitro*
Cholinesterase inhibition	Developmental toxicity	Rapid prototype: testicular toxicity
Bladder urothelial hyperplasia	Teratogenicity	–
Cardiotoxicity	Testicular toxicity	–

Likelihood	Explanation
Certain	**= Endpoint is considered for classification**
Probable	
Plausible (baseline)	
Equivocal	
Doubted	The weight of evidence opposes the proposition.
Improbable	There is at least one strong argument that the proposition is false and there are no arguments that it is true.
Impossible	There is proof that the proposition is false.
Open	There is no evidence that supports or opposes the proposition.
Contradicted	There is proof that the proposition is both true and false.

Prediction	Explanation
Inactive prediction	The query structure does not match any structural alert for bacterial *in vitro* mutagenicity in Derek. Additionally, the query structure does not contain any unclassified or misclassified features.
Inactive prediction with misclassified features	Features of the query structure were found in the Lhasa Ames test reference set and have been observed in mutagens that do not match bacterial *in vitro* mutagenicity structural alerts in Derek. The relationship between these features and mutagenic activity may be coincidental or contributory.
Inactive prediction with unclassified features	The query structure contains features that were not found in the Lhasa Ames test reference set and do not match any structural alerts for bacterial *in vitro* mutagenicity in Derek.

3. FIT screening evaluation (v2.0)

Example of a Derek assessment for 'compound X'

Derek predictions (Reasoning summary and alerts found):

- alpha-2-mu-Globulin nephropathy in bacterium is IMPOSSIBLE
- alpha-2-mu-Globulin nephropathy in human is IMPOSSIBLE
- alpha-2-mu-Globulin nephropathy in mammal is DOUBTED
- Carcinogenicity in bacterium is IMPOSSIBLE; Glycidyl ether, amine, ester or amide
- Carcinogenicity in human is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Carcinogenicity in mammal is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Chromosome damage in vitro in bacterium is IMPOSSIBLE; Glycidyl ether, amine, ester or amide
- Chromosome damage in vitro in human is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Chromosome damage in vitro in mammal is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Developmental toxicity in bacterium is IMPOSSIBLE; Epoxide
- Developmental toxicity in human is PLAUSIBLE; Epoxide
- Developmental toxicity in mammal is PLAUSIBLE; Epoxide
- Irritation (of the eye) in bacterium is IMPOSSIBLE; Epoxide
- Irritation (of the eye) in human is PLAUSIBLE; Epoxide
- Irritation (of the eye) in mammal is PLAUSIBLE; Epoxide
- Irritation (of the skin) in bacterium is IMPOSSIBLE; Epoxide
- Irritation (of the skin) in human is PLAUSIBLE; Epoxide
- Irritation (of the skin) in mammal is PLAUSIBLE; Epoxide
- Mutagenicity in vitro in bacterium is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Nephrotoxicity in bacterium is IMPOSSIBLE; 1,2-Ethyleneglycol or derivative
- Nephrotoxicity in human is EQUIVOCAL; 1,2-Ethyleneglycol or derivative
- Nephrotoxicity in mammal is EQUIVOCAL; 1,2-Ethyleneglycol or derivative
- Skin sensitisation in bacterium is IMPOSSIBLE; Glycidyl ether, amine, ester or amide
- Skin sensitisation in human is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Skin sensitisation in mammal is PLAUSIBLE; Glycidyl ether, amine, ester or amide

Toxicological endpoint

Likelyhood level

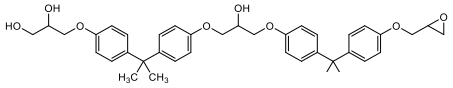
3. FIT screening evaluation (v2.0)

Example of a FIT screening result for 'compound X' in a parenteral application

Compound X

Structure

BADGE dimer-H_2O



[ToxID 5819] $C_{39}H_{46}O_8$ 642.79

FIT Screening Evaluation:

Cramer Classification: Class III

Derek predictions (Reasoning summary and alerts found):

- alpha-2-mu-Globulin nephropathy in bacterium is IMPOSSIBLE
- alpha-2-mu-Globulin nephropathy in human is IMPOSSIBLE
- alpha-2-mu-Globulin nephropathy in mammal is DOUBTED
- Carcinogenicity in bacterium is IMPOSSIBLE; Glycidyl ether, amine, ester or amide
- Carcinogenicity in human is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Carcinogenicity in mammal is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Chromosome damage in vitro in bacterium is IMPOSSIBLE; Glycidyl ether, amine, ester or amide
- Chromosome damage in vitro in human is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Chromosome damage in vitro in mammal is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Developmental toxicity in bacterium is IMPOSSIBLE; Epoxide
- Developmental toxicity in human is PLAUSIBLE; Epoxide
- Developmental toxicity in mammal is PLAUSIBLE; Epoxide
- Irritation (of the eye) in bacterium is IMPOSSIBLE; Epoxide
- Irritation (of the eye) in human is PLAUSIBLE; Epoxide
- Irritation (of the eye) in mammal is PLAUSIBLE; Epoxide
- Irritation (of the skin) in bacterium is IMPOSSIBLE; Epoxide
- Irritation (of the skin) in human is PLAUSIBLE; Epoxide
- Irritation (of the skin) in mammal is PLAUSIBLE; Epoxide
- Mutagenicity in vitro in bacterium is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Nephrotoxicity in bacterium is IMPOSSIBLE; 1,2-Ethyleneglycol or derivative
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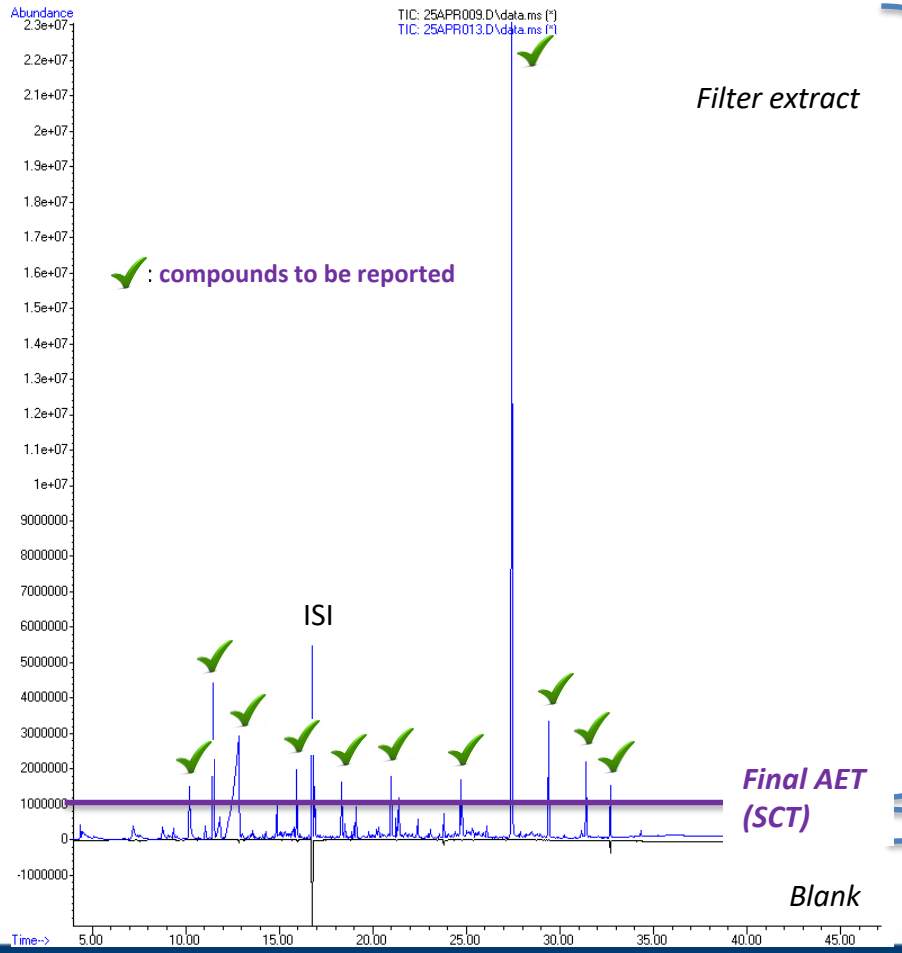
- Nephrotoxicity in mammal is EQUIVOCAL; 1,2-Ethyleneglycol or derivative
- Skin sensitisation in bacterium is IMPOSSIBLE; Glycidyl ether, amine, ester or amide
- Skin sensitisation in human is PLAUSIBLE; Glycidyl ether, amine, ester or amide
- Skin sensitisation in mammal is PLAUSIBLE; Glycidyl ether, amine, ester or amide

FIT Screening Classification: Class III
Suggested Threshold level: 1.5 µg/day

3. FIT screening evaluation (v2.0)

➔ Final AET based on SCT is often used as Reporting Limit in extractables studies

Example 2: filter



Reported compounds

	Result (µg/filter)
COMPOUND #1	100
COMPOUND #2	200
COMPOUND #3	1300
COMPOUND #4	2000
COMPOUND #5	400
COMPOUND #6	250
COMPOUND #7	13000
COMPOUND #8	100
COMPOUND #9	47000
COMPOUND #10	400
COMPOUND #11	100
COMPOUND #12	5500
COMPOUND #13	33000
COMPOUND #14	1200
COMPOUND #15	3500

Compounds not considered for toxicological evaluation

3. FIT screening evaluation (v2.0)

Example 2 (filter - PDP)

- Further calculations will give the **following AET levels for the respective classes**:

Tox endpoint	General tox.	Sensitizer & irritant	Carcinogen
Class	Class I	Class II	Class III
Threshold level (µg/day)	50	5	1.5 (PDP-SCT)
AET (µg/filter)	50 000	5 000	1 500
Final AET (µg/filter)	25 000	2 500	750

*

**

*: calculations → similar as in slide 'Calculation AET – example 2 (filter)'

**: taking into account 50% uncertainty for screening

→ **Final AET values per class can be used for narrowing down the list of extractables**

3. FIT screening evaluation (v2.0)

Example 2 (filter - PDP)

- Narrowing down the list of extractables:

	Class	Threshold for Class (µg/day)	Final AET for Class (µg/filter)		Extractables study Result (µg/filter)
COMPOUND #1	Class I	50	25 000	>	200
COMPOUND #2	Class I	50	25 000	>	400
COMPOUND #3	Class III	1.5	750	<	2600
COMPOUND #4	Class I	50	25 000	>	4000
COMPOUND #5	Class II	5	2 500	>	800
COMPOUND #6	Class I	50	25 000	>	500
COMPOUND #7	Class II	5	2 500	<	26000
COMPOUND #8	Class III	1.5	750	>	200
COMPOUND #9	Class I	50	25 000	<	92000
COMPOUND #10	Class II	5	2 500	>	800
COMPOUND #11	Class III	1.5	750	>	200
COMPOUND #12	Class I	50	25 000	>	11000
COMPOUND #13	Class III	1.5	750	<	66000
COMPOUND #14	Class I	50	25 000	>	2400
COMPOUND #15	Class II	5	2 500	<	7000

Bridging E&L- overview

1. Bridging Extractables and Leachables - basic concept

2. The Threshold approach

    2.1 Organic compounds

        - Safety Concern Theshold (SCT)

        - Threshold of Toxicological Concern (TTC)

    2.2 Elements

        - Permitted Daily Exposure (PDE)

    2.3 Analytical Evaluation Threshold (AET)

3. FIT screening evaluation (v2.0)

    - Subdivision of identified compounds into classes?

    - Derek assessment: rule based SAR assessment

4. Summary

4. Summary

Bridging between EXT and LEA studies?

ID	Class	Threshold for Class (µg/day)	Final AET for Class (µg/filter)	Extractables study Result (µg/filter)	
COMPOUND #1	Class I	50	25000	>	200
COMPOUND #2	Class I	50	25000	>	400
COMPOUND #3	Class III	1.5	750	<	2600
COMPOUND #4	Class I	50	25000	>	4000
COMPOUND #5	Class II	5	2500	>	800
COMPOUND #6	Class I	50	25000	>	500
COMPOUND #7	Class II	5	2500	<	26000
COMPOUND #8	Class III	1.5	750	>	200
COMPOUND #9	Class I	50	25000	<	94000
COMPOUND #10	Class II	5	2500	>	800
COMPOUND #11	Class III	1.5	750	>	200
COMPOUND #12	Class I	50	25000	>	11000
COMPOUND #13	Class III	1.5	750	<	66000
COMPOUND #14	Class I	50	25000	>	2400
COMPOUND #15	Class II	5	2500	<	7000

1. Extractables study:
   - Screen for compounds above final AET (based on SCT of application)
2. Subdivide compounds into different classes with corresponding threshold
3. Evaluate conc of EXT vs. class specific Final AET per compound
4. **Targets requiring further following up during leachables study**

Questions?