Closing the Gap between Extractables and Leachables
A Case Study Approach

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30 Years of experience in Biocompatibility Testing for the Medical Device and the Pharma Industry

FDA Registered, ISO 17025 Accredited, GLP-Certification, GMP-compliant testing

150 Researchers
TOXIKON – COMPANY PROFILE

- *In-vivo* testing services (US)
- *In-vitro* testing services (US, Europe)
- Analytical chemistry (US, Europe)
  *Extractables/leachables*
  *Compendial testing (EP, USP, JP)*
  *Method development/validation*
EXTRACTABLES / LEACHABLES RESEARCH (since 2001)
- Over 1000 E/L-Related Projects in 2009 – 2010
- 45 Employees (10 PhD, 10 Eng, 4 full time QA)
- Dedicated Equipment/Standards For E/L-Testing
- Optimized Procedures/Protocols for E/L-Projects
- Three divisions: 1. Disposables/Single use (in (bio)production)
  2. Parenterals + Ophthalmics
  3. Inhalables (OINDP’s)

NEW DEVELOPMENTS
- Rapid Microbiology Methods
- General Pharmaceutical Support
1. Introduction
2. Leachables: a Subset of Extractables?
3. Consider the Sterilization
4. Consider the Whole Device
5. Consider the Secondary Packaging
6. Consider the Right Choice of Extraction Solvent
7. Consider other Processing Steps
8. Case Study: Even then, Things can go Wrong!
9. Lessons Learned / Conclusion
1. INTRODUCTION
INTRODUCTION: WHY PERFORMING E/L-STUDIES?

- **REGULATORY REQUIREMENT FOR SAFETY ASSESSMENT OF PHARMACEUTICAL CONTAINERS**
  
  1999: FDA: “CONTAINER/CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS”
  2005: EMEA: “GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS”

- **TOXICITY OF IMPURITIES, LEACHING FROM CONTAINERS/CLOSURES**

- May REACT with API, DRUG COMPONENTS

**EXTRACTABLE PROFILE**

*Purpose:* try to identify as many impurities as possible in the materials used for the manufacture of containers.
- Aggressive extraction conditions
- Screening methods

**LEACHABLES PROFILE**

*Purpose:* to identify impurities, leaching from the container into the actual drug product
- Simulated storage conditions (cfr. stability)
- Validated methods

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“Main Extractable” becomes a leachable!!
2. LEACHABLES: A SUBSET OF EXTRACTABLES?
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In early stages of E/L research (5 – 10 years ago):
• Consensus: Leachables are a subset of Extractables
• Extractable study should be designed to identify all potential leachables

FDA and EMA also include this thinking in their Guidelines and Guidances

Migration studies may only be omitted if, based on the outcome of the extraction studies, the calculated maximum amount of individual leachable substance that may be present in the active substance/medicinal product leads to levels demonstrated to be toxicologically safe. When a migration study is not considered necessary and thus is not conducted, a justification should be provided.
2. LEACHABLES: A SUBSET OF EXTRACTABLES?

➡️ THEORY:

extractables

leachables

➡️ PRACTICE:

extractables

leachables

MIND THE GAP!

In the last 5 years, there is a growing consensus that – based upon experimental evidence – **Leachables are not always a subset of Extractables**!!

Yet, a lot of pharma companies adhere to the risk assessment of pharmaceutical containers and closures, solely based upon Extractables Data...
2. LEACHABLES: A SUBSET OF EXTRACTABLES?

➔ THEORY:

extractables
leachables

➔ PRACTICE:

extractables
leachables

CLOSING THE GAP!!
2. LEACHABLES: A SUBSET OF EXTRACTABLES?

TRADITIONAL STEPS IN THE SAFETY EVALUATION OF A PHARMACEUTICAL CONTAINER/CLOSURE

- A well designed EXTRACTABLE STUDY IS THE FIRST STEP IN THE SAFETY ASSESSMENT OF A CONTAINER CLOSURE SYSTEM

- TARGET COMPOUNDS FOR LEACHABLE STUDIES ARE SELECTED BASED UPON THE RESULTS OF EXTRACTABLE STUDIES (Remark: Pharmacopoeial tests are not equivalent to a well-designed extractable study!!)

- LEACHABLES CAN BE CONTROLLED/ASSESSED THROUGH EXTRACTABLES

- USE PLACEBO AS AN EXTRACTION SIMULANT IN EXTRACTABLE STUDIES
4 EXTRACTION STUDIES

The aim of extraction studies is to determine those additives of the material that might be extracted by the preparation or the active substance in contact with the material. Extraction studies are considered to be necessary for plastic material used for container closure systems of non-solid active substances and non-solid dosage forms for oral and topical (except ophthalmic) use if the material is neither described in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, nor has been approved for foodstuff packaging. For non-compendial plastic material used for container closure systems for non-solid medicinal products intended for inhalation, parenteral or ophthalmic administration, extraction studies are required even when approved for use in food packaging.
3. CONSIDER THE STERILIZATION
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CASE STUDY

- Polypropylene Containers, Before and after sterilization (25kGy Beta irradiation)
- Extracted with Dichloromethane
- Ratio: 1 g/ 10 mL, reflux for 8h
- Analysis (presented): LC/MS (APCI-)

Sterilized Material

Unsterilized material

Irganox 1330 degradation

Irganox 1330
3. CONSIDER THE STERILIZATION

IRRADIATION STERILIZATION MAY LEAD TO DEGRADATION OF POLYMER ADDITIVES!!
AGEING - STERILIZATION

POLYMER DEGRADATION (e.g. Scissions, Crosslinking, cyclization)

POLYMER ADDITIVE DEGRADATION (see example for Irganox 1330!)

CHANGES IN POLYMER CRYSTALLINITY

This will impact the: LEACHABLES SOLUBILITY

LEACHABLES MIGRATION

CONCLUSION: TEST FOR EXTRACTABLES AND LEACHABLES ON STERILIZED C/C SYSTEMS
4. CONSIDER THE WHOLE DEVICE
4. CONSIDER THE WHOLE DEVICE

Typical Cases:

- Connectors, Tubing of Administration Set (tubing), Glue, Ports, Filters in I.V. Bag applications (not only film!)

- Silicone Oil, Glue extractables, Extractables from Barrel Manufacture

- Integrated Filter in Sterile Administrations (e.g. Ophthalmic)

- Reconstituting Solution (WFI, 0.9% NaCl), stored in Separate Vial / Syringe

- Cross Contamination during Sterilization (e.g. Autoclaving)

- ....
5. CONSIDER THE SECONDARY PACKAGING
Case study LEA: 100 mL flexible multi-layer bag containing a drug solution ageing at 25°C and 40°C for 3 months
Results for S-VOC (Semi-Volatile Organic Compounds)

Conclusion:
1. MAIN Leachable: bislactone, from adhesive of ALUMINUM Multilayer overwrap!!
2. T increase leads to increased leaching behaviour of additives / degradation products

5. CONSIDER THE SECONDARY PACKAGING
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Typical Cases:

- Overwrap (I.V.-Bags, Monodoses, ...)
- Label migration (Ophthalmic, I.V.-Bags, Polyolefin Containers)
- Ink Migration (I.V.-Bags)
- Needle Shield (Pre-Filled Syringe)

More delicate for Primary Packaging, made of materials with low barrier properties.
6. CONSIDER THE RIGHT EXTRACTION SOLVENT
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CASE STUDY: impact of contact solution on migration / extraction behavior

Extractable study of a POLYOLEFIN CONTAINER, using 3 solvents:
1. Water for Injection (WFI)
2. Drug Product (containing 3% organic material)
3. Ethanol (96%)

Identical extraction conditions for 3 experiments: refluxing for 8 h at 1 bottle/30mL ratio
Only results of GC/MS (semi-volatile compounds) is shown

Solubility of targets in WFI < Solubility of targets in DP << Solubility targets in EtOH
Interaction polymer-WFI < Interaction polymer-DP << Interaction polymer-EtOH

WFI Extract

DP Extract

EtOH Extract
6. CONSIDER THE RIGHT EXTRACTION SOLVENT

CASE STUDY: PROVE OF EQUIVALENCY OF OLD VS NEW MATERIAL

SITUATION 1

PROOF OF EQUIVALENCY WITH WFI

WFI as extraction solvent

2 materials were refluxed for 8 hours in WFI

Extracted with DCM, subseq. concentrated

Analyzed with GC/MS (semi-volatiles)

Conclusion
almost the same extraction profile in WFI!
6. CONSIDER THE RIGHT EXTRACTION SOLVENT

SITUATION 2

DCM as extraction solvent

2 materials were refluxed for 8 hours in DCM

Analyzed with GC/MS (semi-volatiles)

Conclusion:

COMPLETELY DIFFERENT extraction profile in DCM!

MECHANISTIC CONSIDERATIONS

Solubility of targets in WFI  $\ll$  Solubility targets in DCM

Interaction polymer-WFI  $\ll$  Interaction polymer-DCM

ADVISE

Consider relevancy of adding additional solvent!
6. CONSIDER THE RIGHT EXTRACTION SOLVENT

THE CRITICALITY OF USING THE DRUG PRODUCT (VEHICLE) (DP(V)) AS A SOLVENT

Perform E-study in Drug Product (Vehicle), suggested in:

FDA-Container/Closure Guidance (1999), (eg parenteral/Ophthalmic)

- If the extraction properties of the drug product vehicle may reasonably be expected to differ from that of water (e.g., due to high or low pH or due to a solubilizing excipient), then drug product should be used as the extracting medium.

EMEA-Guideline - immediate packaging (2005)

stress conditions to increase the rate of extraction. The solvent used for extraction should have the same propensity to extract substances as the active substance/dosage form as appropriate. In the case of medicinal products the preferred solvent would be the medicinal product or placebo vehicle. The
6. CONSIDER THE RIGHT EXTRACTION SOLVENT

THE CRITICALITY OF USING THE DP(V) AS A SOLVENT

Complex DPV: COMPLEX INTERPRETATION OF E-STUDIES!!
6. CONSIDER THE RIGHT EXTRACTION SOLVENT

THE CRITICALITY OF SELECTING DP(V) AS SOLVENT

Similar advantages/disadvantages as for WFI:

ADVANTAGE: simulation of extractables behaviour in DP(V): same extraction propensity!

DISADVANTAGE: Risk of missing the presence of compounds

- Matrix interference of DP(V) (see previous slide)

Risk of misinterpretation of analytical data

- DP(V) Matrix degradant may be misinterpreted as extractable!

Risk of underestimating the concentration of compounds

- Extraction conditions – may potentially be to mild
  - Difficult to select the right set of extraction conditions (e.g. extraction time, temperature!)

EXAMPLE for DP(V) – does 8 hour reflux mimic a 3 year shelf life?
6. CONSIDER THE RIGHT EXTRACTION SOLVENT

THE CRITICALITY OF SELECTING DP(V) AS SOLVENT

ADVICE when selecting DP(V) as extraction solution:

1. Combine it with organic model solvent (e.g. IPA, DCM, Hexane)
   - Minimize the risk of missing the presence of extractables

2. If necessary: Use validated methods, developed for extraction study with DP(V) as solvent
   - Eliminate matrix interference from DP(V) matrix
   - Assess DP(V) matrix degradation during extractable study

3. Consider the right set of extraction conditions, relevant for the DP(V) contact
   - Extraction time
   - Temperature
7. CONSIDER THE PROCESSING STEPS
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CASE STUDY: Leachable Study on a **vial system** (vial + rubber)
Using **Validated Methods** for Target Compounds, defined after
Extractable Study + **Screening Method** (unexpected compounds)

RESULTS: 3 leachables were detected: 2 target compounds, 1 non-
target compound (no increase in concentration over time)

Origin of non-target Compound:
Sterile Filtration prior to filling in the PFS!
7. CONSIDER THE PROCESSING STEPS

Typical Cases:

- Filtration
- Tubing for Filling
- Storage Containers of Excipients
- Intermediate Storage of API
- Lyophilization Equipment
- Cross Contamination during Sterilization (e.g. autoclaving)
- Inner/Outer layer cross contamination of Films.
- Diptubes in Storage Containers
- ....
8. EVEN THEN, THINGS CAN GO WONG!!
The more we know, the more we know we don’t know!

Anonymous
Berlin, 2012
Prefilled Glass Syringe
Filled with WFI
Stored for 3y at 25°C/60% R.H.
Initial Extractables Study on Plunger (WFI, IPA)
Leachables (Screening) Analyses after 3 years
   Headspace GC/MS: Volatiles
   DCM extraction + GC/MS: Semi-Volatiles
   DCM extraction + LC/MS (APCI+/−): Non-Volatiles

6 different Combinations (Syringe/Plunger/Needle Shield) were tested.

Results: for Semi-Volatiles, indicative for other groups of compounds
RESULT OF WFI EXTRACTABLE STUDY OF THE PLUNGER

Chromatogram of Extractable Study in WFI

Conditions:
Reflux 8h, ratio 1g /10 mL
DCM extraction of WFI, concentration step of DCM, followed by GC/MS analysis for Semi-Volatiles Analysis

12 COMPOUNDS AT RELATIVELY LOW CONC.
RESULT OF **IPA EXTRACTABLE STUDY** OF THE PLUNGER

Chromatogram of Extractable Study in IPA
Conditions:
Reflux 8h, ratio 1g /10 mL

3 COMPOUNDS AT RELATIVELY LOW [CONC]
8. EVEN THEN, THINGS CAN GO WRONG

RESULT OF THE LEACHABLE STUDY OF THE WFI-PREFILLED SYRINGE
3 YEARS AT 25°C – 60% R.H.
LEACHABLES: compounds originating from:

1. Rubber Plunger
2. Hydrolyzed Compounds from Rubber Plunger
3. Compounds from Needle Shield
4. Hydrolyzed/Oxidized Compounds from Needle Shield
5. A lot of “Unknown” Compounds, both identity and origin is not clear
6. Results are independent of Type of Rubber / Rubber Manufacturer of the Rubber Plunger!!

Concentration range: from 10 µg/L to > 10 mg/L!
Observations when comparing the results of the Extractable Studies on the Rubber Plunger with the Leachable studies on the PFS system

- **Concentrations of Leachables was Higher** than the Extractables found with WFI as an Extraction Solvent

- Also for more **Aggressive solvents** (e.g. IPA), **not a good match** between Extractables and Leachables

- The observation was **independent of the type of rubber**
How can we try to explain these results?

**Extractable Studies: Temperature Dependence of Diffusion**

By heating up the material (boiling conditions), diffusion of extractables is increased.

\[
\frac{dC}{dt} = D \frac{d^2C}{dx^2}
\]

With \( D = \text{Diffusion coefficient} \)

\[ D = D_0 \exp(-E/RT) \]

This means that a temperature increase from Room Temperature to solvent boiling point will lead to an increase of \( D \) of approx. 2 orders of magnitude (*reference for typical D values: H. Zweifel, « Plastic Additives »*)

Or reflux extraction of 8h will mimic approx. 800h (=33d of R.T. contact)
8. EVEN THEN, THINGS CAN GO WRONG

Extractable Studies: Interaction between Solvent - Material

SOLVENT CAN "PLASTICIZE" or "SWELL" POLYMER: SOLVATED LAYER

ENHANCED DIFFUSION OF LEACHABLES

ACCELERATED LOSS

For Rubbers: Hexane, DCM and IPA will show enhanced diffusion because of the solvent-material interaction

Completeness of extraction can be checked via Asymptotic Extraction Behaviour

Not to the same extent for WFI!
What is not investigated (sufficiently) in an extractable study?

1. **MATERIAL DEGRADATION** (ageing)

2. The **REACTION** (WFI: hydrolysis / O₂: oxidation) of the leachables with the Drug Product (solution)

3. The **EFFECT OF LONG TERM CONTACT** between the drug product and the material
What is not investigated (sufficiently) in an extractable study?

1. MATERIAL DEGRADATION – ASTM 1980 – 02:

Material Degradation: In general ASTM 1980 can be a “general” guidance

\[ AAF = Q_{10} \left( \frac{T_{AA} - T_{RT}}{10} \right) \]

AAF: Accelerated Aging Factor
\( Q_{10} \): Aging factor (10°C increase in T)

\( T_{AA} \): Accelerated Aging Temperature
\( T_{RT} \): Room temperature

8h at 100°C (eg. Refluxing in WFI) represents 1440h (60 days) of RT ageing
8h at 80°C (eg. Refluxing in IPA) represents 15 days of RT ageing

REMARK: Ageing of material is not always representative (Aqueous Environment versus Air (Oxygen!))

8. EVEN THEN, THINGS CAN GO WRONG
What is not investigated (sufficiently) in an extractable study?

2. The REACTION of the Leachables with the Drug Product

EXAMPLE (OXIDATION):

Dissolved Oxygen in WFI /DP(V) will Oxidize Irganox 1076 over time!

Occurrence of “oxaspiro” as a leachable is much more frequent than as an extractable!
What is not investigated (sufficiently) in an extractable study?

2. The REACTION of the Leachables with the Drug Product

\[
\text{BHT} \xrightarrow{\text{H}_2\text{O}} \text{BHT-OH}
\]

*HYDROLYSIS*

*BHT-OH is seldom seen as an extractable, but it is regularly seen as a leachable!*
8. EVEN THEN, THINGS CAN GO WRONG

What is not investigated (sufficiently) in an extractable study?

3. LONG TERM CONTACT between drug product - material

Cresol containing drug products, Bromocresol may be formed in the presence of Bromobutyl Stoppers (Mechanism is unknown)

\[
\text{H}_3\text{C} - \text{C}_6\text{H}_4\text{OH} \xrightarrow{} \text{H}_3\text{C} - \text{C}_6\text{H}_4\text{BrOH}
\]
<table>
<thead>
<tr>
<th>KINETICS OF</th>
<th>Extraction</th>
<th>Extraction</th>
<th>Accelerated Leachable St.</th>
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<td>H₂O e.g. 8h reflux</td>
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**EXTRACTION**

- SLOW – Incomplete
  - no swelling/enhanced diffusion

- FAST – complete
  - Enhanced Diffusion
  - Almost Asymptotic

- Enhanced
  - Diffusion controlled leaching is T-dependent
  - \( D = D_0 \exp(-E/RT) \)

**MATERIAL DEGRADATION**

- Slightly enhanced
  - ASTM 1980: reflux at 100°C/8h: 60d at RT
  - Even if they will be formed, will they come out?

- Very Slightly enhanced
  - ASTM 1980: (IPA) reflux at 80°C/8h: 15d at RT

- Enhanced
  - ASTM 1980: 6 Mo ageing at 40°C \( \equiv \) 17 Mo at 25°C

- SLOW, but evaluated over LONG period! (e.g. 3y)

**REACTION KINETICS**

- Slightly enhanced
  - Low [extr]₀ will limit the formation of reaction comp. (i.e. for slow reactions)

- Not relevant!

- Enhanced,
  - \( k = k_0 \exp(-E_a/RT) \)
  - \( E_a \): Activation Energy, reaction dependent
  - (Pseudo) first order kinetics

- SLOW, but evaluated over LONG period! (e.g. 3y)
9. LESSONS LEARNED
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1. Consider All Components of the Pre-Filled Syringe

2. Consider the Secondary Packaging (Needle Shield), the Processing Conditions, the right set of Conditions to perform the Extractable Study

3. Do not rely solely on Extractable Studies to perform a risk assessment of your Containers/Closures

   *Even if the Guidelines themselves suggest that this could be sufficient*

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<table>
<thead>
<tr>
<th>Description</th>
<th>Overall general description of container closure system, plus:</th>
</tr>
</thead>
<tbody>
<tr>
<td>For Each Packaging Component:</td>
<td>• Name, product code, manufacturer, physical description</td>
</tr>
<tr>
<td></td>
<td>• Materials of construction (for each: name, manufacturer and product code)</td>
</tr>
<tr>
<td></td>
<td>• Description of any additional treatments (e.g., procedures for sterilizing and depyrogenating packaging components)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suitability</th>
<th>Protection: (By each component and/or for the container closure system, as appropriate)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>• Light exposure, when appropriate</td>
</tr>
<tr>
<td></td>
<td>• Reactive gases (e.g., oxygen)</td>
</tr>
<tr>
<td></td>
<td>• Moisture permeation (powders)</td>
</tr>
<tr>
<td></td>
<td>• Solvent loss (liquid-based dosage forms)</td>
</tr>
<tr>
<td></td>
<td>• Sterility (container integrity) or unexposed bioburden</td>
</tr>
<tr>
<td></td>
<td>• Seal integrity or leak testing of tubes (ophthalmics)</td>
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<th>Safety: (for each material of construction, as appropriate)</th>
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<td>• Chemical composition of all plastics, elastomers, adhesives, etc.</td>
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<tr>
<td>• For elastomeric closures: USP Elastomeric Closures for Injections testing</td>
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<td>• For glass components: USP Containers: Chemical Resistance — Glass Containers</td>
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<tr>
<td>• For plastic components and coatings for metal tubes: USP Biological Reactivity Tests</td>
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<td>• If the total weight of extracts significantly exceeds the amount obtained from water extraction, then an extraction profile should be obtained.</td>
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<tr>
<td>• For plastic or elastomeric components undergoing heat sterilization, it is current practice to request that the extraction profile be obtained at 121°C/1 hour using an appropriate solvent.</td>
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**EMEA**

Migration studies may only be omitted if, based on the outcome of the extraction studies, the calculated maximum amount of individual leachable substance that may be present in the active substance/medicinal product leads to levels demonstrated to be toxicologically safe. When a migration study is not considered necessary and thus is not conducted, a justification should be provided.
9. LESSONS LEARNED

3. If Safety Assessment is made on Extractables Results: check off with Leachable Studies!
   *This will account for “unaccounted” leachables, such as polymer degradation, polymer additive degradants, process leachables, secondary packaging, or other extractables missed because of an ill designed study set-up*

4. Consider – if possible – an additional **Accelerated Leachable study** (e.g. with screening methods) to verify the presence of “unexpected leachables” *(as a step in between extractable studies and full leachable studies)*

5. If the above is not possible: add a **screening step in the full leachable study**
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**REACTION KINETICS**

- SLOW, but evaluated over LONG period! (e.g. 3y)
ACKNOWLEDGEMENTS

✓ Dr. Lothar Habel (study director parenterals/injectables)
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✓ Ilse Janssen (LC/MS)
✓ Cindy Claes (Sample prep.)
✓ Pieter Bruyninckx (Sample prep.)
✓ All other staff involved in the studies presented
ANY QUESTIONS?

For further questions, please contact: piet.christiaens@toxikon.be