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Printed paper and board: Priority setting strategy for toxicological assessment

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Food Packaging Forum Workshop

Zürich, 5 October 2017

Overview

- Introduction
- Prioritisation strategy
  - Step 1: Database compilation
  - Step 2: *In silico* prediction
  - Step 3: Literature review
  - Step 4: *In vitro* experiments
- Conclusion and future perspectives

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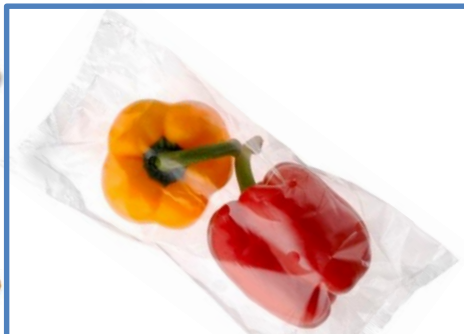
Food contact materials (FCM)



Harmonised EU regulation

Printed paper and board FCM

- Widespread and frequent use
- No specific harmonised European regulation
- Thousands of non (recently) safety-evaluated substances
- Major cause of food contamination by FCM

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PRIORITISATION based on genotoxic potential
using alternative methods (*in silico*, *in vitro*)

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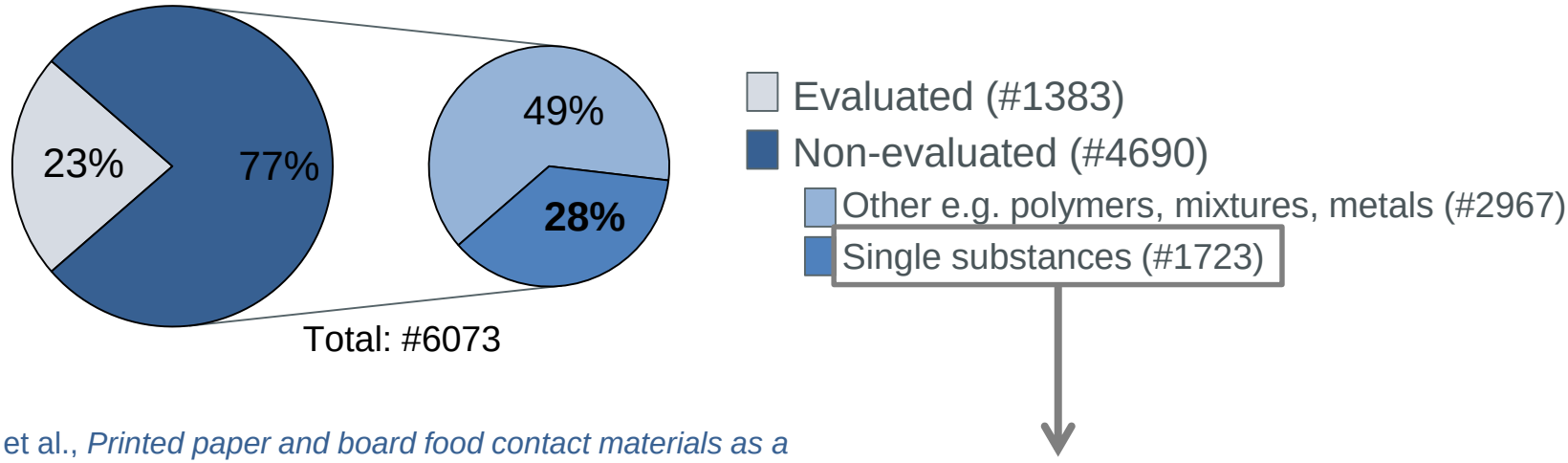
Step 1:
database
compilation

National legislations and European inventories on printing ink and paperboard compounds

- Swiss Ordinance RS 817.023.21 Annex 6 on printing inks (2013)
- Council of Europe resolution on paper and board (2009)
- European Food Safety Authority report on non-plastic FCM (2011)
- EU Regulation 10/2011 on plastic FCM (2016)



Van Bossuyt et al., *Printed paper and board food contact materials as a potential source of food contamination*. Reg. Tox. Pharm., 81 (2016) 10-19

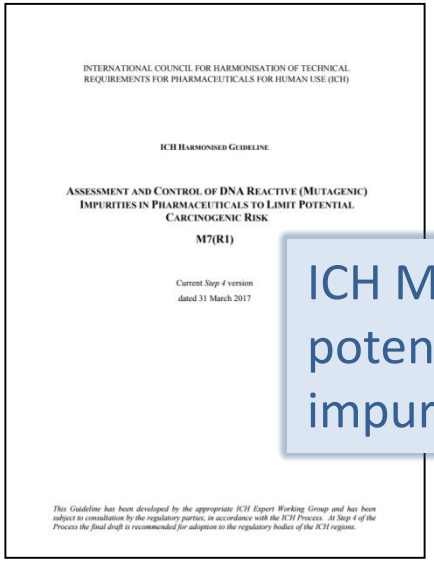
Step 1: database compilation

Step 2: *in silico* prediction

(**Q**uantitative) **S**tructure-**A**ctivity **R**elationship ((Q)SAR)

SAR: qualitative, based on **structural alerts** (SA) or **expert rules**

QSAR: quantitative, based on **mathematical** formula



INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH)

ICH HARMONISED GUIDELINE

ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK

M7(R1)

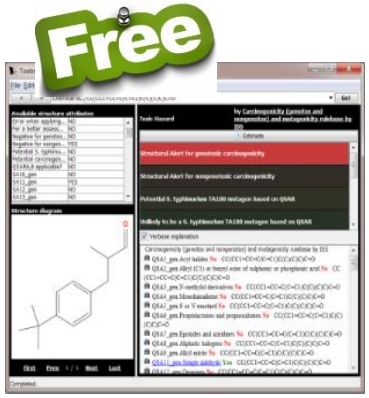
Current *Step 4* version
dated 31 March 2017

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the ICH regions.

ICH M7(R1) guideline on potentially genotoxic impurities in pharmaceuticals

Step 1: database compilation

Step 2: *in silico* prediction

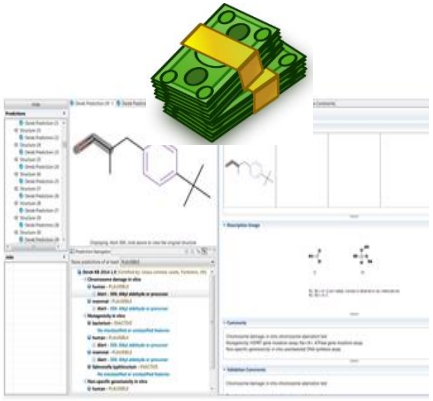


Toxtree (SAR)

v. 2.6.0

VEGA (QSAR)

v. 1.1.1



Derek Nexus™ (SAR)

v. 4.1.0

Sarah Nexus™ (QSAR)

v. 1.2.0

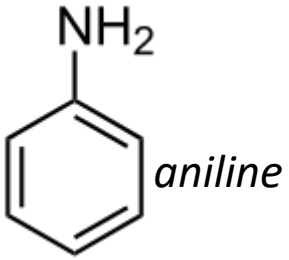
Complementary

- Availability: free – commercial
- Method: SAR – QSAR
- Result representation and explanation: supporting evidence, experimental results, confidence score, applicability domain assessment,…

Step 1: database compilation → **Step 2:** *in silico* prediction

Required: **S**implified **M**olecular-**I**nput **L**ine-**E**ntry **S**ystem (SMILES) representation

E.g. for aniline: C1=CC=C(C=C1)N



aniline

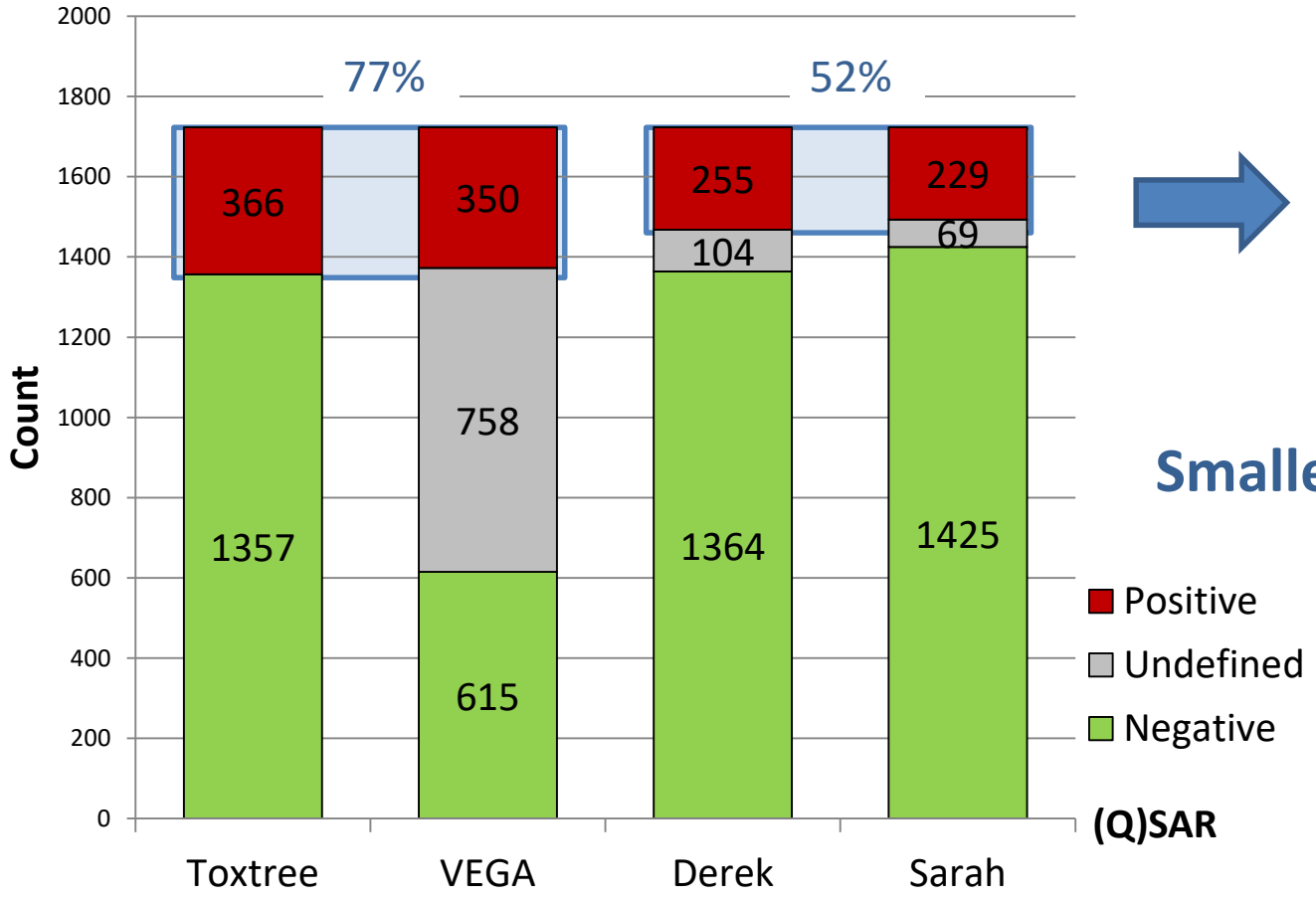
Can be retrieved from:

- www.chemspider.com (Royal Society of Chemistry)
- www.pubchem.ncbi.nlm.nih.gov/- (National Institutes of Health)
- www.chem.sis.nlm.nih.gov/chemidplus/ (National Institutes of Health)
- …

Step 1: database compilation

Step 2: *in silico* prediction

INDIVIDUAL MODELS



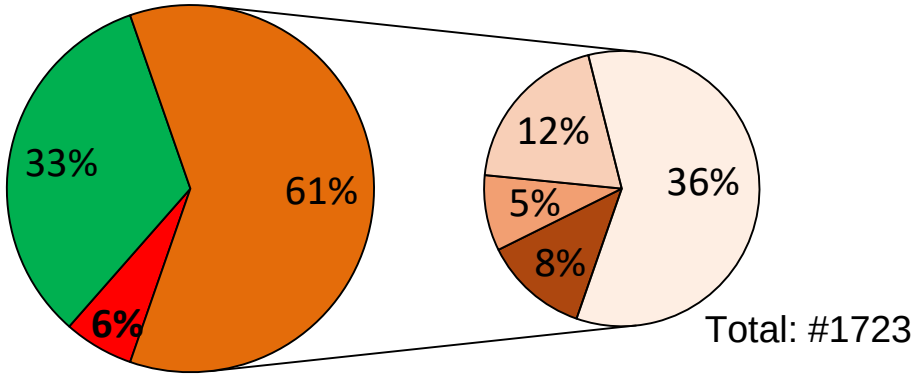
13.5 up to 21% mutagenic

Overlap?

Smaller than expected

Step 1: database compilation → **Step 2:** *in silico* prediction

COMBINED MODELS



- Negative in all models (#572) — **LOWEST PRIORITY**
- Indeterminate (#1045)
  - Negative in all, with restrictions (#619)
  - Mutagenic in 1 (#204)
  - Mutagenic in 2 (#93)
  - Mutagenic in 3 (#129)

  — **MEDIUM PRIORITY**
- Mutagenic in all models (#106) — **HIGHEST PRIORITY**

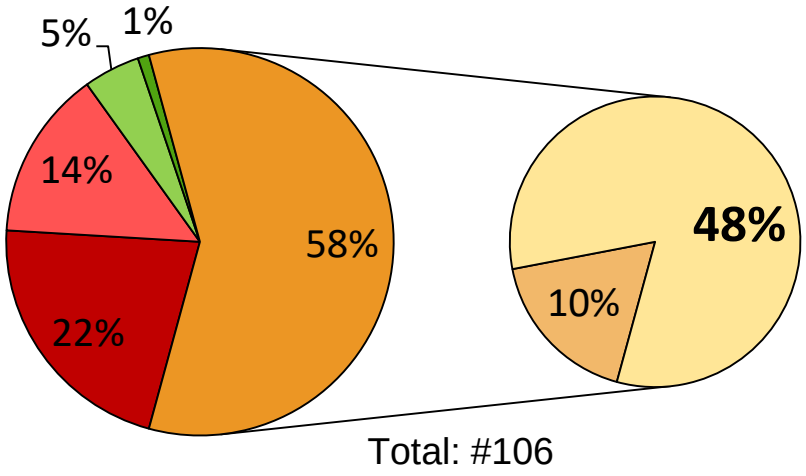
53 are training set compounds = *in vitro* mutagen

Van Bossuyt et al., *(Q)SAR tools for priority setting: A case study with printed paper and board food contact material substances*. Food Chem. Tox., 102 (2017) 109-119

Step 1: database compilation → **Step 2:** *in silico* prediction → **Step 3:** Literature review

Publically available *in vitro* and *in vivo* mutagenicity data

- OECD eChemPortal
- European Chemicals Agency website
- Cosmetic Ingredients database



17 training set mutagens
20 not available → not used?
13 *in vitro* experiments

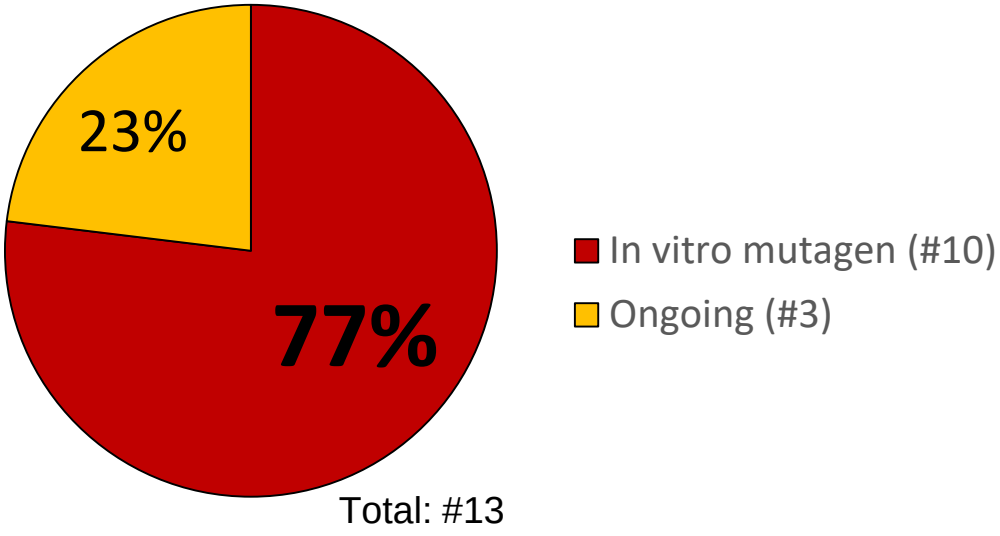
- Negative *in vivo*, official evaluation (#1)
- Negative *in vitro*, no official evaluation (#5)
- More data required (#61)
  - Incomplete data (#11)
  - No data (#50)
- Mutagenic *in vitro*, no *in vivo* follow-up (#16)
- Mutagenic *in vivo* (#23)

Step 1: database compilation | **Step 2:** *in silico* prediction | **Step 3:** Literature review | **Step 4:** *In vitro* experiments

In vitro gene mutation test in bacteria (=Ames test)

ONGOING

Mutagenicity of prioritised printed paper & board substances in *S. typhimurium* strain TA100 and TA98



So far, 10 out of 13 (77%) substances are mutagenic *in vitro*

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- A database was assembled including **6073 substances that can be used in printed paper and board FCM**
- A battery of *in silico* (Q)SAR tools **predicted 106 substances to be mutagenic** *in vitro*
- Publically available literature data showed that minimum **39 of these are experimentally mutagenic**, at least *in vitro*
- Substances without literature data are being **tested *in vitro* and, so far, they are all mutagenic**
- Future steps: **Current usage? Migration?**
- **Prioritisation strategy can be extended** to other substance types/groups

ISP WIV

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