



Development of a novel scoring system for identifying emerging chemical risks in the food chain

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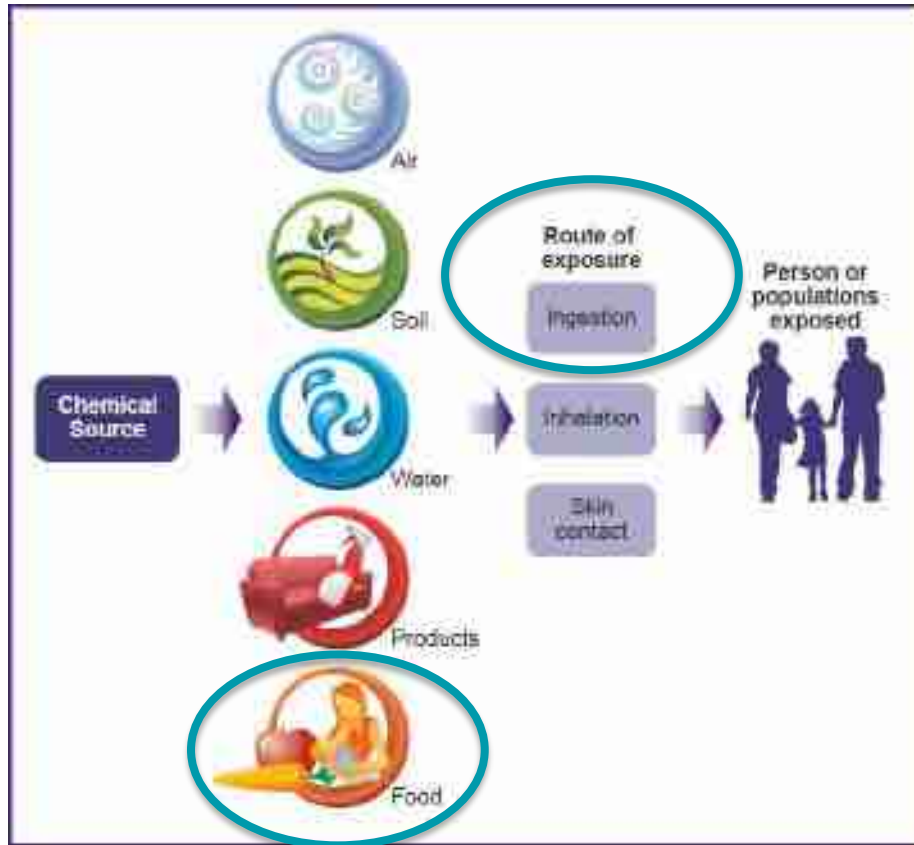
BACKGROUND: CHEMICALS IN OUR ENVIRONMENT



■ Some numbers...

- more than 140,000 chemicals estimated on the EU market
- 19,466 substances registered under REACH (source ECHA, 27/04/2018)
- The Toxic Substances Control Act (TSCA) in the USA lists ~85,000 chemicals
- ~700 new chemicals added to TSCA every year

HUMAN EXPOSURE

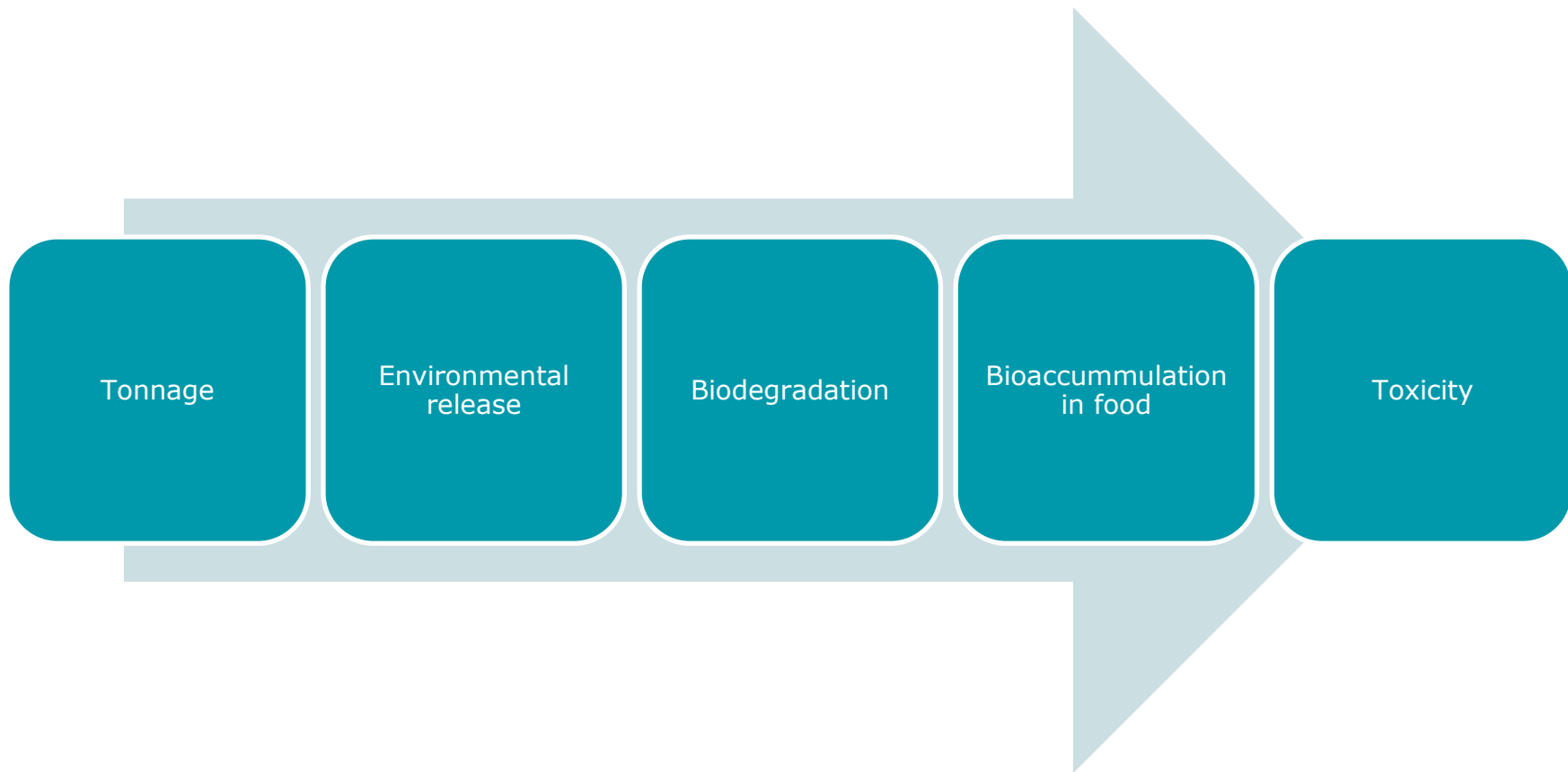


Source: Health Canada

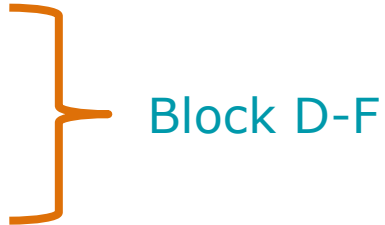
AIM OF THE INVESTIGATION

- To develop a **procedure** for the identification of emerging chemical risks in the food and feed chain
 - covers 'human exposure via the environment' (EU TGD, REACH) only
 - does not cover human exposure to these chemicals via other pathways, e.g. chemicals used in food contact materials or in food processing

GENERAL APPROACH



OVERVIEW OF METHODOLOGY

- Substance selection
 - Endpoints covered
 - Block A: Environmental exposure
 - Block B: Biodegradation
 - Block C: Bioaccumulation in food
 - Block D: Repeated dose toxicity
 - Block E: Reproductive and developmental toxicity
 - Block F: Genotoxicity (carcinogenicity)
 - Scoring, weighting and ranking
 - Maximum score of 10 in each block
 - Four blocks in total, since maximum of blocks D-F is taken
 - Aggregation across all four blocks -> total score (weighting)
- 

METHODOLOGY: BLOCK A (ENVIRONMENTAL EXPOSURE)

- REACH registration tonnage and environmental release categories (ERCs) extracted by ECHA for the 100 substances
- Score for Block A (max. 10) = Tonnage Score + ERC score (max. 5 each)

Upper end REACH registration tonnage [tpa]	Score
≥ 100 000 000	5
10 000 000-99 999 999	5
1 000 000-9 999 999	4
100 000-999 999	3
10 000-99 999	2
<10 000	1

ERC no.	ERC description	Score ¹
4	Industrial use of processing aids	5
8A	Wide dispersive indoor use of processing aids, open	5
8D	Wide dispersive outdoor use of processing aids, open	5
10B	Wide dispersive outdoor use of long-life articles, high or intended release	5
11B	Wide dispersive indoor use of long-life articles, high or intended release	5
5	Industrial inclusion into or onto a matrix	2.5
6D	Industrial use of auxiliaries for polymerisation	1.75
3	Formulation in materials	1.5
12B	Industrial processing of articles with abrasive techniques (high release)	1
8C	Wide dispersive indoor use, inclusion into or onto a matrix	0.75

- Limitation: Tonnage and ERC are not linked

Score block A: 1 + 5 = 6

METHODOLOGY: BLOCK B (BIODEGRADATION)

Interpretation of the results ^a	Score
Readily biodegradable	1
Readily biodegradable, but failing 10-d window	2
Inherently biodegradable	4
Inherently biodegradable, fulfilling specific criteria	4
Inherently biodegradable, not fulfilling specific criteria	6
Not readily biodegradable	8
Not inherently biodegradable	10
Under test condition no biodegradation observed	10

METHODOLOGY: BLOCK B (BIODEGRADATION)

- Reliable experimental data from ECHA CHEM extracted via OECD's eChemPortal
- Problems in data retrieval: hits depend on query; limitation of hits
- Problems in evaluation: diverging results per substance

Substance	Section	Reliability	Interpretation of results
95-48-7	Biodegradation in water: screening tests	2 (reliable with restrictions)	readily biodegradable
95-48-7	Biodegradation in water: screening tests	2 (reliable with restrictions)	inherently biodegradable
95-48-7	Biodegradation in water: screening tests	2 (reliable with restrictions)	readily biodegradable
95-48-7	Biodegradation in water: screening tests	2 (reliable with restrictions)	under test conditions no biodegradation observed
95-48-7	Biodegradation in water: screening tests	2 (reliable with restrictions)	inherently biodegradable
Substance	Section	Reliability	Interpretation of results
85535-85-9	Biodegradation in water: screening tests	2 (reliable with restrictions)	other: not readily biodegradable
85535-85-9	Biodegradation in water: screening tests	2 (reliable with restrictions)	other: not readily biodegradable
85535-85-9	Biodegradation in water: screening tests	2 (reliable with restrictions)	other: not readily biodegradable
85535-85-9	Biodegradation in water: screening tests	2 (reliable with restrictions)	other: not readily biodegradable
85535-85-9	Biodegradation in water: screening tests	2 (reliable with restrictions)	other: not readily biodegradable

- Several evaluation options analysed: 'most frequent' result taken
- Result 'other: not readily biodegradable...' taken as not readily biodegradable

METHODOLOGY: BLOCK C (BIOACCUMULATION IN FOOD)

- ACC-HUMANsteady (implemented in MS Excel®)
- All input data can be predicted by QSAR Toolbox, e.g. log Kow, log Koa, biotransformation half-lives
- Concentrations predicted in:

Food category	Fish		Meat & milk products				Fruit and vegetables					
	planktivore ^(a)	piscivore ^(a)	beef cattle	milk cow	milk	dairy products	Fruit ^(a)	Leaf ^(a)	Root ^(a)	Tuber ^(a)		
Food/feed item							apple	grain	lettuce	grass ^(b)	carrot	potato

- Default scenario coded in ACC-HUMANsteady
- Relative concentrations used for scoring in each food item and grass
- Maximum score in any food item taken as final score for block C

Czub G and McLachlan MS, 2004: *Environmental Toxicology and Chemistry*, 23, 2356-2366
 Undeman E and McLachlan MS, 2011: *Environmental Science & Technology*, 45, 8429-8436

METHODOLOGY: BLOCK D-F (TOXICITY)

Repeated dose toxicity (block D)	Score
NOAEL 0-10 mg/kg bw (toxic)	10
NOAEL 10-100 mg/kg bw (moderately toxic)	5
NOAEL 100-10,000 mg/kg bw (low toxicity)	1
Reproductive and developmental toxicity (block E)	
Classification as Repr. 1a, 1b and 2	10
Evidence for developmental or reproductive toxicity	10
No evidence for developmental or reproductive toxicity	1
Genotoxicity (block F)	
Classification as Muta. 1a, 1b and 2	10
Evidence for in vivo genotoxicity	10
Evidence for in vitro genotoxicity	10
Only ambiguous findings (both in vitro or in vivo)	5
Negative and ambiguous findings (both in vitro or in vivo)	5
Only negative findings	1

METHODOLOGY: BLOCK D-F (TOXICITY)

- Reliable experimental data from ECHA CHEM extracted via OECD's eChemPortal
 - Repeated dose toxicity: NOAEL in chronic or sub-chronic studies
 - Reproductive toxicity: WoE assessment of key studies
 - Genotoxicity: *in vitro* and *in vivo* studies
- Problems in data retrieval: hits depend on query; limitation of hits
- Problems in curation/evaluation: dose conversions, time-consuming, diverging results per substance -> most conservative taken

METHODOLOGY: BLOCK D-F (TOXICITY)

- Reproductive/developmental toxicity: manual evaluation required (no study IDs in data extracted via eChemPortal -> maternal and fetal data could not be aligned)
- Also: classification according to CLP Regulation (**C**lassification, **L**abelling and **P**ackaging) for CMR properties taken (**C**arcinogenic, **M**utagenic, **R**eprotoxic)

RESULTS BLOCK A-F

Substance Name	Final Score			
	Block A	Block B	Block C	Max. (Block D-F)
Positive controls				
<i>p,p'</i> -DDT	10	10	10	10
PCBs	10	10	10	10
Pentabromodiphenyl oxide (BDE-99)	10	10	10	10
Decabromodiphenyl ether (BDE-209)	8	10	10	10
Cyclohexanemethanamine, 5-amino-1,3,3-trimethyl-	8	10	10	5
Tris(1-chloro-2-propyl) phosphate	8	10	10	5
Chloroform	9	10	3	10
1,1-Dichloroethene	8	10	1	10

**How do we combine scores
from the different blocks?**

WEIGHTING SCENARIOS – PIVOT TABLE SELECTION

Name (CAS no.)	Block A Score	Tonnage (tpa)	Block B Score	Block C Score	Toxicity Score
10H-Phenothiazine	7	10000	10	10	10
3,3',3'',5,5',5''-Hexa-tert-butyl- α,α',α'' -(mesityleni	7	10000	10	10	5
6-Phenyl-1,3,5-triazine-2,4-diamine	5.5	100000	10	10	10
Alkanes, C14-17, chloro	8	100000	8	6	10
Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)	7	10000	10	10	10
Cyclohexanemethanamine, 5-amino-1,1,1-trimethyl	8	100000	10	10	5
Decabromodiphenyl ether (BDE-209)	8	100000	10	10	10
Dibutyltin oxide	7	10000	10	10	10
p,p'-DDE	10	0	10	10	10
PCBs	10	0	10	10	10
Pentabromodiphenyl oxide (BDE-60)	10	0	10	10	10
Terphenyl hydrogenated	7	10000	10	6	10
Tris(1-chloro-2-propyl) phosphate	8	110000	10	10	5
Total					

Block A

10

8

7

5.5

4.5

3.4

2.8

1

0.5

0.25

0.1

0.15

Block B

10

8

4

1

7

Block C

10

0

3

1

Toxicity block

10

5

1

- Three of the four positive controls rank high
- BDE-209 already assessed by EFSA: one of the highest dietary exposures among BDEs evaluated
- Specific accumulation of TCPP in carrots predicted by ACC-HUMANsteady also shown experimentally

WEIGHTING SCENARIOS – RANKING

- **Risk** is defined as the probability that **exposure** to a **hazard** will lead to a negative consequence
- Risk = **Exposure** x **Hazard**

One example:

Total Score (WS) = $[(\text{Score block A} \times \text{Score block B}) + \text{Score block C2}] / 20 \times \text{MAX Score (blocks D-F)}$

WEIGHTING SCENARIOS – RANKING

Name	CAS #	Score block A	Score block B	Score block C	Max. Score blocks D-F	Total Score (WS) ^b
Decabromodiphenyl ether (BDE-209)	1163-19-5	8	10	10	10	90
Dibutyltin oxide	818-08-6	7	10	10	10	85
10H-Phenothiazine	92-84-2	7	10	10	10	85
Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, octadecyl ester	2082-79-3	7	10	10	10	85
6-Phenyl-1,3,5-triazine-2,4-diamine	91-76-9	5.5	10	10	10	78
Ammonium perchlorate	7790-98-9	4.5	10	10	10	73
Pigment green 7	68987-63-3	4.5	10	10	10	73
4,6-Bis(octylthiomethyl)-o-cresol	110553-27-0	4.5	10	10	10	73
2,2-Dimethylpropane-1,3-diol	126-30-7	9	1	3	5	4.5
2-Ethyl-1-hexanol	104-76-7	9	1	3	5	4.5
4-Methyl-2-pentanone	108-10-1	8	1	3	5	4.3
Glutamic acid, sodium salt	142-47-2	2.25	1	6	0	1.9
1,2-Pentanediol	5343-92-0	7	2	3	0	1.2
n-Tridecane	629-50-5	8	1	3	0	0.85
Tetradecane	629-59-4	8	1	3	0	0.85
Benzyl acetate	140-11-4	7	1	3	0	0.80

CONCLUSIONS

- Extraction, curation and evaluation of data from REACH registration dossiers is possible in principle, but encountered several problems:
 - Curation/evaluation is very time consuming for human health endpoints
 - Manual evaluation is required for reproductive toxicity
- Predictions for biodegradation very good agreement (in scoring system)
- ACC-HUMANsteady software for bioaccumulation:
 - Extremely useful (11 food items)
 - New approach, incorporating e.g. biotransformation half lives

CONCLUSIONS

- All input data required for biodegradation, bioaccumulation and toxicity predictions can be obtained from a single software (QSAR Toolbox)
- Main limitation: all models primarily developed for neutral hydrophobic substances; applicability to other compounds (e.g. metals, inorganic and ionisable compounds) uncertain
- Output: pivot table or ranking

What next?



APPLICATION OF PROCEDURE TO REACH DATABASE

- All registered substances to be extracted from the ECHA CHEM database
- QSAR Toolbox profilers and profiling results used for selection of eligible substances + removal of duplicates, etc..
- Assessment of Blocks A-F
- Project to be completed by end 2018



FOR MORE INFORMATION

EXTERNAL SCIENTIFIC REPORT

FoBiG 

APPENDIX 03 June 2016

Final report: Testing a procedure for the identification of emerging chemical risks in the food chain

External scientific report. OC/EFSA/SCER/2014/03

¹Fraunhofer ITEM, ²FoBiG

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Environmental Science Processes & Impacts



PAPER

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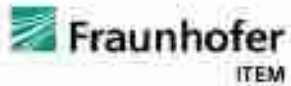
Development of a novel scoring system for identifying emerging chemical risks in the food chain

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