In Silico Approaches for TTC Assessment

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Abbreviations (1)

- CERES—Chemical Evaluation and Risk Estimation System
- CP-ANN—Counter-Propagation Artificial Neural Network
- ECHA—European Chemicals Agency
- EPA—Environmental Protection Agency
- EFSA—European Food Safety Authority
- FDA—Food and Drug Administration
- ILSI—International Life Sciences Institute
- Jmax—Maximal flux (across the skin)
- MSDI—Maximised Survey-derived Daily Intake
- NO(A)EL—No Observed (Adverse) Effect
Abbreviations (2)

- NTP—National Toxicology Program
- PBBK—Physiologically Based Biokinetic
- QSAR—Quantitative Structure-Activity Relationship
- SCCS—Scientific Committee on Consumer Safety
- SA—Structural Alert
- ToxRefDB—Toxicity Reference Database
- TTC—Threshold of Toxicological Concern
Overview

- A Threshold of Toxicological Concern (TTC) decision tree
- Computational tools for the application of the TTC approach
- Chemoinformatics in the development of the TTC approach
  - Quality-controlled datasets for modelling
  - Investigation of chemical space
  - Identification and use of chemotypes
- Route to route extrapolation
  - COSMOS-ILSI decision tree for oral to dermal extrapolation
  - Internal TTC approach and biokinetic modelling
- Take home messages
Threshold of Toxicological Concern for Non-Cancer Effects

- Correlation of structural (Cramer) class with chronic toxicity (NOELs)
- 613 organic chemicals
- Munro et al. (1996)

<table>
<thead>
<tr>
<th>Cramer class</th>
<th>Fifth percentile NOEL (mg/kg bw per day)</th>
<th>TTC value (mg/kg bw per day)</th>
<th>TTC value (µg/kg bw per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>3.0</td>
<td>0.03</td>
<td>30</td>
</tr>
<tr>
<td>II</td>
<td>0.91</td>
<td>0.009</td>
<td>9</td>
</tr>
<tr>
<td>III</td>
<td>0.15</td>
<td>0.0015</td>
<td>1.5</td>
</tr>
</tbody>
</table>
1. Is the substance a non-essential metal or metal containing compound, or is it a polyhalogenated-dibenzo(dioxin, -dibenzofuran, or -biphenyl)?

2. Are there structural alerts that raise concern for potential genotoxicity?

3. Is the chemical an aflatoxin-like-, azoxy-, or N-nitroso- compound?

4. Does estimated intake exceed TTC of 0.15 µg/day?

   - Negligible risk (low probability of a life-time cancer risk greater than 1 in 10^6 – see text)

5. Does estimated intake exceed TTC of 1.5 µg/day?

6. Is the compound an organophosphate?

7. Does estimated intake exceed TTC of 18 µg/day?

8. Is the compound in Cramer structural class III?

9. Does estimated intake exceed 90 µg/day?

10. Is the compound in Cramer structural class II?

11. Does estimated intake exceed 540 µg/day?

12. Does estimated intake exceed 1800 µg/day?

   - Substance would not be expected to be a safety concern

Risk assessment requires compound-specific toxicity data

Cancer endpoints

High potency carcinogen

Non-cancer endpoints

Structural alert for genotoxicity

Organophosphate neurotoxicant

Kroes decision tree

Benigni-Bossa Rules for Genotoxicity & Carcinogenicity

Structural Alerts (SAs)
- 30 SAs for genotoxic carcinogens
- 5 SAs for non-genotoxic carcinogens

Three QSAR models

\[
\text{Probability of effect} = F_{\text{Hydrophobic}} + F_{\text{Electronic}} + F_{\text{Steric}}
\]
CAESAR Mutagenicity Model

- Statistically-based
- Support Vector Machine classification + some SAs from Benigni-Bossa
- Training set: 4225 compounds from the Kazius-Bursi database
- Part of VEGA suite of models

http://www.caesar-project.eu

http://www.vega-qsar.eu
Danish (Q)SAR Database

QSAR Predictions for > 600,000 chemicals

> 200 QSARs

Physicochemical, ADMET, fate and ecotoxicity

http://qsar.food.dtu.dk
Class III: high oral toxicity
Class II: intermediate
Class I: low oral toxicity ("innocuous")

- Decision tree containing 33 (Y/N) questions applied in sequence
- Three important considerations:
  1. Structural features associated with toxicity
  2. Ease of metabolism (and thus elimination)
  3. Natural occurrence in body or in traditional foods

Toxtree

- Downloadable versions from JRC and Sourceforge: [http://toxtree.sourceforge.net](http://toxtree.sourceforge.net)
- Current version 2.6.6 (June 2014) includes Cramer, Cramer with Extensions, genotoxicity and carcinogenicity (Benigni-Bossa, In Vivo Micronucleus, Ames), Kroes
- Toxtree online: [http://toxtree.sf.net/predict](http://toxtree.sf.net/predict)

**Compound structure**

**Compound properties**

**Prediction**

**Reasoning**

**Structure diagram**

- Q1. Normal constituent of the body **No** vinclozolin
- Q2. Contains functional groups associated with enhanced toxicity **No** vinclozolin
- Q3. Contains elements other than C, H, C, N, divalent **Yes** vinclozolin
- Q4. Elements not listed in Q3 occurs only as a Na, K, Ca, Mg, N salt, sulphamate, sulphonate, sulphate, hydrochloride
  - **No** Class **High (Class III)** vinclozolin
OECD QSAR Toolbox

http://www.qsartoolbox.org
Example: Alpha Ionone

- CAS 127-41-3
- SMILES: CC1=CCCC(C1/C=C/C(=O)C)(C)C (from chemspider.com)
- Maximised Survey-derived Daily Intake (MSDI): 270 µg/p/day
Example: Alpha Ionone

- Benigni-Bossa (from Toxtree): SA for genotoxic carcinogenicity
- Mutagenicity QSAR (Danish database): 10 negative, 1 positive
- Experimental *in vitro* mutagenicity and chromosome aberration: negative
- Experimental *in vivo* micronucleus: negative
- Cramer Class I (from Toxtree)
  - TTC for genotoxic carcinogens is 1.5 µg / person / day
  - TTC for Cramer Class I is 1800 µg / person / day
  - MSDI of 270 µg/p/day < TTC of 1800 µg/p/ day for Cramer Class I
1. Select Decision Tree
2. View Decision Tree
3. Find the Right Chemical Structure

ChemSpider
Search and share chemistry

Found 2 results
Search term: alpha-ionone Spelling corrected using CaffeineFix from alpha ionone. (Found by synonym)

(E)-4-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-3-buten-2-one

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula</td>
<td>C₉H₁₄O</td>
</tr>
<tr>
<td>Average mass</td>
<td>192.297 Da</td>
</tr>
<tr>
<td>Monoisotopic mass</td>
<td>192.151413 Da</td>
</tr>
<tr>
<td>ChemSpider ID</td>
<td>4445317</td>
</tr>
</tbody>
</table>

View on ChemSpider: [http://www.chemspider.com](http://www.chemspider.com)

More details:

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic name</td>
<td>(3E)-4-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-3-buten-2-one</td>
</tr>
<tr>
<td>SMILES</td>
<td>CC1=CCCC(C1/C=C/C(-O)C)(C)C</td>
</tr>
<tr>
<td>Std. InChI</td>
<td>InChI=1S/C13H20O/c1-10-6-5-9-13(3,4)12(10)8-7-11(2)14/h6-8,12H,5,9H2,1-4H3/b8-7+</td>
</tr>
<tr>
<td>Std. InChIKey</td>
<td>UZELPKABPNNA-BQYQJAHWSA-N</td>
</tr>
</tbody>
</table>
4. Enter Structure and “Estimate”

5. Evaluate Reasoning

1N, 2N, 3N, 5N, 6N, 7N, 16N, 17N, 19N, 23N, 24Y, 18N
6. “Save” Results

<table>
<thead>
<tr>
<th>Structure</th>
<th>Properties</th>
</tr>
</thead>
</table>
| ![Chemical Structure](image) | cdk:Comment = Created from SMILES  
SMILES = CC1=CCCC(C1/C=C/C(=O)C)(C)C  
Cramer rules = Low (Class I)  
toxTree.tree.cramer.CramerTreeResult =  
1N,2N,3N,5N,6N,7N,16N,17N,19N,23N,24Y,18N |
## Evaluation of Pesticide Metabolites

### Table 1: Isoxazuron metabolites

<table>
<thead>
<tr>
<th>Compound identifier</th>
<th>Name in Study and Assessment reports and SMILES</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>Isoxazuron CC(O)C1ccc(N(=O)N(C(O))cc1</td>
<td>![Structure Image]</td>
</tr>
<tr>
<td>M02</td>
<td>AE F064145 Monodesmethyl isoxazuron CC(C)C1ccc(N(=O)C)cc1</td>
<td>![Structure Image]</td>
</tr>
<tr>
<td>M03</td>
<td>RPA 41044 Hydroxy-monodesmethyl CC(C)(O)C1ccc(N(=O)C)cc1</td>
<td>![Structure Image]</td>
</tr>
<tr>
<td>M04</td>
<td>RPA 410365 Hydroxy-didesmethyl CC(C)(O)C1ccc(N(=O)(C))cc1</td>
<td>![Structure Image]</td>
</tr>
<tr>
<td>M05</td>
<td>RPA 409656 CC(C)C1ccc(N(=O)N)cc1C(O)=O</td>
<td>![Structure Image]</td>
</tr>
<tr>
<td>M06</td>
<td>RPA 410198 CC(O)=O=C1ccc(N)cc1</td>
<td>![Structure Image]</td>
</tr>
<tr>
<td>M07</td>
<td>RPA 410226, sum of isomers CC(O)C1cccN(=O)N(C)cc1</td>
<td>![Structure Image]</td>
</tr>
<tr>
<td>M07a, M07b</td>
<td>BD-236D2 (Isomer 1), RPA 410226</td>
<td>![Structure Image]</td>
</tr>
<tr>
<td>M08</td>
<td>RPA 409658-1-OH-isoxazuron CC(C)C1ccc(N(=O)N)cc1</td>
<td>![Structure Image]</td>
</tr>
</tbody>
</table>

### Compound identifier | Name in Study and Assessment reports and SMILES | Structure |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M09</td>
<td>BD-236D7 Hydroxypropyl isoxazuron CC(C)(O)C1ccc(N(=O)C)cc1</td>
<td>![Structure Image]</td>
</tr>
<tr>
<td>M10</td>
<td>LS 730334 Didesmethyl isoxazuron CC(C)C1ccc(N)(=O)cc1</td>
<td>![Structure Image]</td>
</tr>
<tr>
<td>M11</td>
<td>BD-236D3 RPA 409660 CC(C)C1ccc(N(=O)(C))cc1</td>
<td>![Structure Image]</td>
</tr>
<tr>
<td>M12</td>
<td>BD-236D4 CN(C)(=O)N=C1ccc(CCO)cc1</td>
<td>![Structure Image]</td>
</tr>
</tbody>
</table>

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**SCIENTIFIC OPINION**

Guidance on the establishment of the residue definition for dietary risk assessment

EFSA Panel on Plant Protection Products and their Residues (PPR)

European Food Safety Authority (EFSA), Parma, Italy

Comments to EFSA by 2 May

Evaluation of Toxtree–Cramer

- Many of the original Cramer rules are written in a confusing and inter-dependent way
- Two rules are not based on chemical features, but simply make reference to look-up lists of chemicals (Q1, normal body constituents; Q22, common food components)
- Some rules make ambiguous references to chemical features (e.g., “steric hindrance,” “simply branched”)
- Several studies have identified outliers (e.g., Class I compounds that have low NOELs)
- A revised/alternative classification scheme should be more discriminating in terms of NOEL values

→ need to update Cramer classification scheme

Lapenna & Worth (2011). JRC report EUR 24898 EN
Q1: Normal constituent of the body? No    Q2
Q2: Any of these functional groups: aliphatic sec-amine, cyano, N-nitroso, diazo, triazeno, or quaternary N? No    Q3
Q3: Any elements other than C, H, O, N, divalent S? No    Q5
Q5: Simply branched acyclic aliphatic hydrocarbon or a common carbohydrate? No    Q6
Q6: Benzene derivative...? No    Q7
Q7: Heterocyclic? No    Q16
Q16: Common terpene? No    Q17
Q17: Readily hydrolyzed to a common terpene, alcohol, aldehyde or carboxylic acid?

Toxtree  Yes

Q19: Yes
Q20: Yes
Q21: No
Q18: Yes    Class II (Intermediate)

QSAR ToolBox  No

Q19: No
Q23: No
Q24: No
Q25: No
Q26: No
Q22: No
Q33: No    Class III (High)

Q18: Is it "an acyclic aliphatic ketone, ketal or ketoalcohol with no other functional groups and with four or more carbon atoms on either side of the keto group"?
Cramer Classifications:
Two Computer-Based Predictions vs. Expert Judgement

COSMOS Project

New Toxicological Databases

Threshold of Toxicological Concern

PBPK and In Vitro – In Vivo Extrapolation

In Silico Models

http://www.cosmostox.eu
COSMOS Database

- Open-access
- High-quality chemical and toxicity data
- User-friendly query builder (chemical name, structure, toxicity data)
- Cosmetics Inventory
  - 44,765 unique chemical structures
  - 12,538 toxicity studies for 1,660 compounds across 27 endpoints
- oRepeatTox DB toxicity data (230 cosmetics-related chemicals and 340 studies)
- Skin permeability data (v2) (470 chemicals)

Webinar and tutorial:
http://www.cosmostox.eu/what/COSMOSdb/

http://cosmosdb.cosmostox.eu
COSMOS Cosmetics Inventory

- Over 5,500 substances
- 66 unique use functions
COSMOS TTC Dataset—Quality Process

1. Toxicity database

2. NO(A)EL database

3. TTC dataset

Study inclusion criteria
- Oral ≥ 28 day
- Reproductive, developmental
- Mouse, rat, dog, primate, rabbit

- Study reliability
- NOAEL selection criteria
  - Chronic NOAELs preferred
  - Lowest NOAEL with clear LOAEL

NOAEL decision
- Expert review of 25% of the study results
- 10th percentile
- Large differences between different data sources
## COSMOS TTC Dataset v1.8

<table>
<thead>
<tr>
<th>Compound classes</th>
<th>COSMOS TTC v1.8</th>
<th>Munro</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>552</td>
<td>613</td>
</tr>
<tr>
<td>Cosmetics inventory</td>
<td>495</td>
<td>190</td>
</tr>
<tr>
<td>Cramer Class distribution-I</td>
<td>39%</td>
<td>22%</td>
</tr>
<tr>
<td>Cramer Class distribution-III</td>
<td>53%</td>
<td>73%</td>
</tr>
</tbody>
</table>

### Cramer Class Distribution

<table>
<thead>
<tr>
<th>Cramer Class</th>
<th>COSMOS</th>
<th>Munro</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Histogram</strong></td>
<td><strong>5(^{th}) % POD (mg/kg-bw/day)</strong></td>
</tr>
<tr>
<td>I</td>
<td><img src="image" alt="Histogram" /></td>
<td>4.152 (N=217)</td>
</tr>
<tr>
<td>II</td>
<td><img src="image" alt="Histogram" /></td>
<td>0.581 (N=40)</td>
</tr>
<tr>
<td>III</td>
<td><img src="image" alt="Histogram" /></td>
<td>0.769 (N=295)</td>
</tr>
<tr>
<td>Structural Features</td>
<td>MUNRO</td>
<td>COSMOS (v1.8)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------</td>
<td>---------------</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol, phenol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol - 1,1; 1,2; 1,3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldehyde</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amine, aromatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halides, organo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorus containing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonyl (S=O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyran ring, generic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organosilicon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chain - aliphatic chain &gt;= C8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chain - oxyalkane (EO-PO)</td>
<td></td>
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<tr>
<td>Surfactants - nonionic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surfactants - anionic</td>
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<td></td>
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<tr>
<td>Surfactants - cationic</td>
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<tr>
<td>Carbohydrate</td>
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<tr>
<td>Steroid ring</td>
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<tr>
<td>Parabens</td>
<td></td>
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</tr>
<tr>
<td>Phthalates</td>
<td></td>
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</tr>
<tr>
<td>Hair-dyes - amine_ethanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair-dyes - amine_bis_ethanol</td>
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<td></td>
</tr>
<tr>
<td>Hair-dyes - azo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair-dyes - benzene_amino_nitro_alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair-dyes - benzene_diamino</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair-dyes - benzene_nitro</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chemical space – structural features

- > 4x organohalides
- > 3x phosphorus
- > 2x urea
- Steroid ring

% in dataset (ratio)
Chemotypes

- Structural fragments with atom/bond properties
  (partial charges, polarizability, electronegativity, etc.)
- Improved prediction of reactivity and toxicity (compared with structural alerts)
- Example: association of diazoles and triazoles with cleft palate formation

\[
\text{Pi charge} < \text{zero} \quad \text{Sigma charge} > \text{zero}
\]

X = nitrogen or carbon
The Chemotyper

- **The Chemotyper**
  - Feature searching
  - Profiling datasets/inventories
  - Building prediction models

- **ToxPrint**
  - Library of public chemotypes
  - Generic fragments
  - Genotoxic carcinogens (Ashby-Tennant)
  - Cancer TTC (Kroes et al)

Publicly available from:
Chemotyper: https://www.chemotyper.org
ToxPrint: https://toxprint.org

Developed by Altamira LLC and Molecular Networks GmbH under FDA contract
### Relating Chemotypes to Potency Classes

<table>
<thead>
<tr>
<th>Categories</th>
<th>Frequency</th>
<th>Potency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>carboxylicAcid_generic</td>
<td>0</td>
<td>-2.03</td>
</tr>
<tr>
<td>carboxylicEster_alkyl</td>
<td>20</td>
<td>-1.26</td>
</tr>
<tr>
<td>aldehyde_generic</td>
<td>40 (%)</td>
<td>-3.35</td>
</tr>
<tr>
<td>amine_aldehyde_alkyl</td>
<td>0</td>
<td>1.54</td>
</tr>
<tr>
<td>amine_alkyl_ethylalolamine</td>
<td>20</td>
<td>2.28</td>
</tr>
<tr>
<td>amine_pri-NH2_aromatic</td>
<td>40 (%)</td>
<td>1.94</td>
</tr>
<tr>
<td>amine_sec-NH_aromatic</td>
<td>0</td>
<td>1.63</td>
</tr>
<tr>
<td>amine_ter-N_aliphatic</td>
<td>20</td>
<td>1.07</td>
</tr>
<tr>
<td>ether_aliphatic</td>
<td>40 (%)</td>
<td>-2.79</td>
</tr>
<tr>
<td>ether_aliphatic_aromatic</td>
<td>0</td>
<td>1.18</td>
</tr>
<tr>
<td>alcohol_aliphatic_generic</td>
<td>20</td>
<td>2.07</td>
</tr>
<tr>
<td>alcohol_diol_(1,2-)</td>
<td>40 (%)</td>
<td>-3.91</td>
</tr>
<tr>
<td>alcohol_pri-alkyl</td>
<td>0</td>
<td>0.61</td>
</tr>
<tr>
<td>alcohol_sec-alkyl</td>
<td>20</td>
<td>1.12</td>
</tr>
<tr>
<td>halide_alkyl-X_generic</td>
<td>40 (%)</td>
<td>1.63</td>
</tr>
<tr>
<td>halide_aromatic-X_generic</td>
<td>0</td>
<td>0.97</td>
</tr>
<tr>
<td>azo_aromatic</td>
<td>20</td>
<td>-1.12</td>
</tr>
<tr>
<td>sulfur_oxide</td>
<td>40 (%)</td>
<td>-2.50</td>
</tr>
<tr>
<td>sulfonylamide</td>
<td>0</td>
<td>-2.49</td>
</tr>
<tr>
<td>alkaneLinear_dodecyl_C12</td>
<td>20</td>
<td>-2.18</td>
</tr>
<tr>
<td>alkaneLinear_octyl_C8</td>
<td>40 (%)</td>
<td>2.05</td>
</tr>
<tr>
<td>aromaticAlkane_Ph-C1_acyclic_generic</td>
<td>0</td>
<td>1.65</td>
</tr>
<tr>
<td>ligand_path_4_bidentate_aminoe</td>
<td>20</td>
<td>-3.21</td>
</tr>
<tr>
<td>hetero_[5]_O_oxolane</td>
<td>40 (%)</td>
<td>1.09</td>
</tr>
<tr>
<td>hetero_[6]_N_pyridine_generic</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Potency: Z-score of NOAEL distribution

**Legend:**
- **Dark orange:** most potent
- **Light orange:** more than average
- **Grey:** average potency
- **Light blue:** less than average
- **Dark blue:** least potent

**Note:**
- Dark orange: Most potent
- Light orange: More than average
- Grey: Average potency
- Light blue: Less than average
- Dark blue: Least potent

**Potency Calculation:**
- Potency: Z-score of NOAEL distribution

**Frequency Categories:**
- 0: 20%
- 20%
- 40%

**Graph:**
- X-axis: Categories
- Y-axis: Frequency (%)
Dermal TTC Values

- 140 chemicals with dermal NO(A)ELs
- 5th percentile for CC III = 5.0 mg/kg bw/d (cf, 0.15)
- 5th percentile for CC I = 35.3 mg/kg bw/d (cf, 3.0)

COSMOS-ILSI
Decision Tree

- Compare dermal dose with oral TTC value
- Series of corrections to applied dose
- Systemic dose = \( J_{\text{max}} \cdot \text{Area} \cdot \text{time} \)
- \( J_{\text{max}} \) from *in vitro* study, QSAR prediction or PBBK simulation
- Refine ingredient concentration (< saturation)
- Consider hydrolysis / metabolism

Biologically-Based Modelling for an Internal TTC

Take Home Messages

- Various software tools are available to apply the TTC approach
- Computational predictions are not the solution - expert judgement required
- Computational methods also provide a means of further developing the TTC approach
- Chemistry-based modelling can be supplemented with biological modelling
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