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Thresholds of Toxicological Concern (TTC): Human Toxicology

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The Threshold of Toxicological Concern

The TTC concept embodies the notion that for a non-tested substance an exposure exists below which there is no significant risk to human health and as a consequence does not need to be further evaluated by toxicity studies.

The TTC approach provides a tool to assess the potential risk to HH related to exposure to a chemical using:

- **available data (including chemical structure plus any in vitro, in vivo and/or in silico information)**
- **information on potential exposure**
- **the predicted in vivo toxicity based on (chronic) toxicity data of compounds of similar chemical structures**

It is an example for Integrated Testing Strategy

Evolution of the TTC Concept for Application to Substances in Food

- **Frawley (1967) first proposed a TTC concept for substances intended for use in food-packaging materials**
- **Munro et al. (1990) determined that a dietary level of 1 ppb for food packaging materials would not pose an appreciable risk**
- **Rulis (1992) proposed a value of 0.5 ppb (equivalent to 1.5 µg daily intake) for indirect food additives, which was subsequently adopted by the U.S. FDA in 1995 as the "threshold of regulation" for compounds that are not known to be carcinogens and do not contain structural alerts indicative of carcinogenicity.**

Present Uses of the TTC-Approach

- US Food and Drug Administration in the regulation of food contact materials (USFDA, 1995)
- EFSA and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in evaluations of flavouring substances.

Its use has been proposed for

- Herbal preparations (EMEA, 2007)
- Personal and household care products (Blackburn et al., 2005)
- Impurities in pharmaceuticals (Müller et al., 2005).
- Cosmetic ingredients and impurities (Kroes et al., 2007).

Munro et al (1996, 2004) evaluated a wide variety of non-carcinogenic substances of divergent structure using JECFA Monographs, NTP Studies, IRIS Database, DART Database. Applied criteria are:

- **Well-defined chemical structure**
- **Non-tumorigenic endpoints**
- **Minimum 60-day duration unless teratogenicity or reproduction study**
- **Oral exposure**
- **Study conducted in rodents or rabbits**
- **LOEL as well as NOEL, some with NOEL only**

2,944 NOELs on 612 substances have been identified and the NOELs distributed to the three classes of Cramer et al 1978.

The “Cramer“ Classes for non-genotoxic compounds

CLASS I = simple structures efficiently metabolized to innocuous products; anticipated low order of oral toxicity

CLASS II = intermediate structures; less innocuous than substances in Class I, but no positive indication of toxic potential

CLASS III = complex structures; metabolism to reactive products suggestive of potential toxicity

(Cramer et al Fd Cosmet Toxicol 16, 255-276, 1978)

Establishment of “Cramer Classes”

To consider structural alerts a 33 steps decision tree has been developed to attribute compounds to one of the 3 classes of decreasing . For example:

1. Is the compound a normal constituent of the body? **(I)**
2. Does it contain an aliphatic secondary amine, cyano-, N-nitroso, diazo, triazeno or quarternary nitrogen? **(III)**

5. Is it a simply branched acyclic aliphatic? **(I)**

13. Does the ring bear any substituents? **(III)**

26. Is it a cyclopropane or cyclobutane with aliphatic side chains or only alcohol, aldehyde, acid, ester? **(II)**

Calculation of Human Exposure Threshold

The fifth percentile NOEL of the 2,944 NOELs was calculated for each structural class and the safety factor of 100 was applied.

Cramer Class	5th percentil NOEL (mg/kg bwt)	Expos. Threshold (mg/day)*
I	3.0	1.8
II	0.91	0.54
III	0.15	0.09

* Exposure calculated for 60 kg bwt. (Munroe et al 1996)

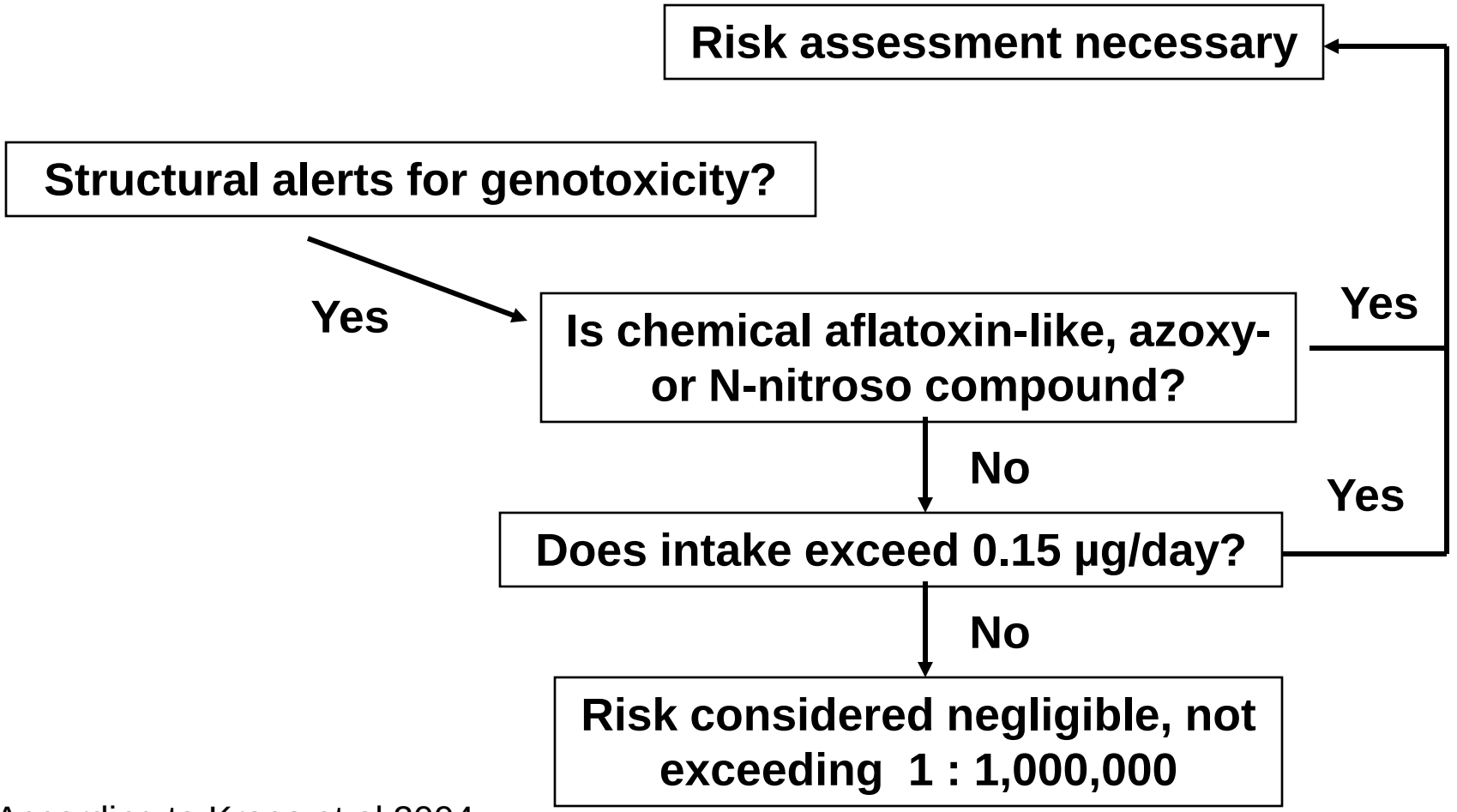
Approaches to Substances with Structural Alerts for Genotoxicity

Kroes et al. (2004) proposed a TTC value of 0.15 µg/day for substances with structural alerts for potential genotoxicity, except for aflatoxin-like substances and azoxy- and N-nitroso compounds (most potent genotoxic carcinogens).

The value of 0.15 µg/day was derived from analysis of 10^{-6} risks for approximately 730 compounds having carcinogenicity data.

This and the other TTCs have been incorporated into a broader decision tree scheme for risk assessment of substances present at low levels in the diet.

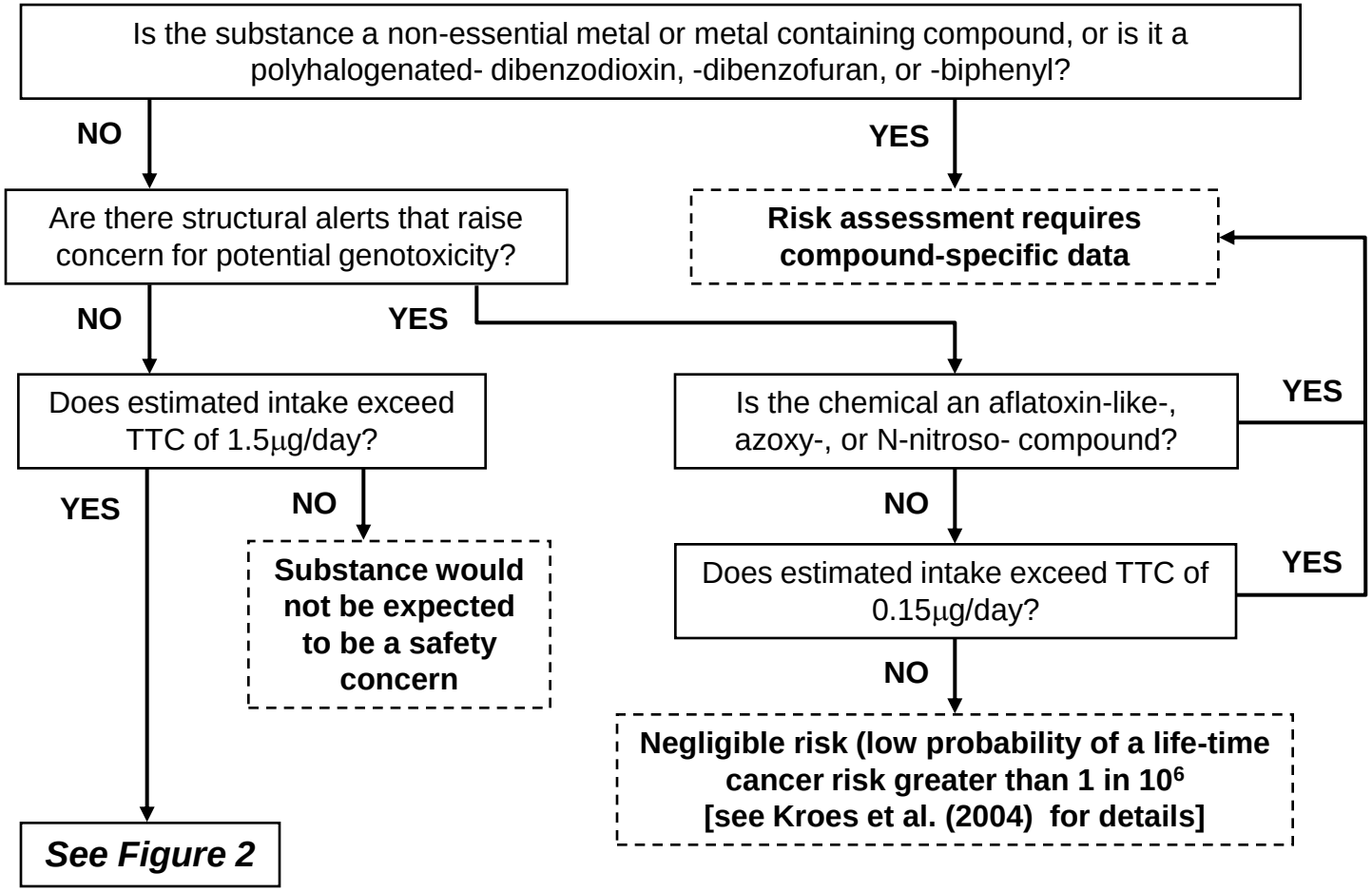
Approaches to Substances with Structural Alerts for Genotoxicity

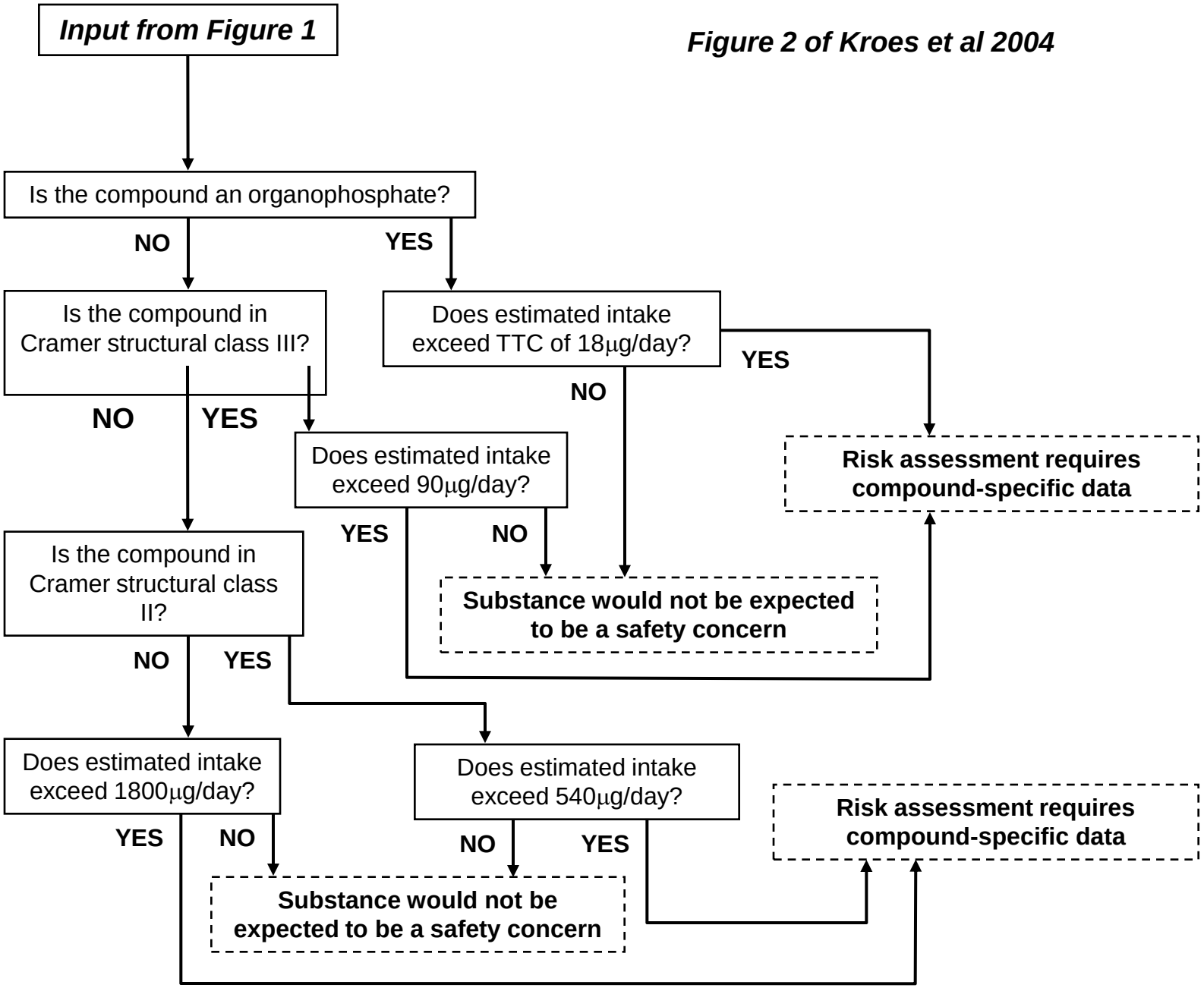


According to Kroes et al 2004

Refinement of TTC approach by by Kroes et al 2004

Figure 1




Input from Figure 1
Figure 2 of Kroes et al 2004
Is the compound an organophosphate?
NO
YES
Is the compound in Cramer structural class III?
Does estimated intake exceed TTC of 18μg/day?
YES
NO
NO
YES
Does estimated intake exceed 90μg/day?
Risk assessment requires compound-specific data
YES
NO
Is the compound in Cramer structural class II?
Substance would not be expected to be a safety concern
NO
YES
Does estimated intake exceed 1800μg/day?
Does estimated intake exceed 540μg/day?
Risk assessment requires compound-specific data
YES
NO
NO
YES
Substance would not be expected to be a safety concern

The TTCs for Food (oral exposure)

Genotoxic Carcinogens: 0.15 μg/day

Genotoxic impurities in human oral drugs: 1,5 μg/day

Organophosphates: 18 μg/day

All other substances: 90, 540 or 1,800 μg/day for Cramer classes I , II and III of increasing toxicity calculated by Munro et al 1996.

The approach has been refined by Kroes et al. 2004

The recently proposed TTC concept for cosmetics considers rates of dermal absorption and duration of exposure (Kroes et al 2007).

TTC for Cosmetics (Kroes et al 2007)

- Similarity between cosmetic ingredients and the chemicals on which the Cramer classes for chemicals in food were based.
- Differences in metabolism between the dermal and oral routes of application.
- Default adjustment factors for percutaneous penetration.
- Default adjustment factors for percutaneous penetration to assess the systemic exposure for rinse off products.
- Default adjustment factors for intermittent use of cosmetic products resulting in intermittent human exposure.
- Total (aggregate) exposure to the ingredient.
- Simultaneous exposure to different cosmetic ingredients.

Proposed default adjustment factors for the % dose absorbed across the skin (cosmetic ingredients)

Jmax (Microg/cm2/h)	Default% dose absorbed per 24 h
Non-reactive chemicals with MW larger 1000	Negligible
Up to 0.1	10
Between 0.1 and 10	40
Beyond 10	80

Jmax: maximum flux

Kroes et al: Fd Chem Toxicol 45, 2533-2562, 2007

Default Factors for Skin Absorption of Cosmetics

Compounds	Times oral TTC
MW > 500, log P_{OW} < -1 to >4; solvents or substances insoluble in water	10
MW < 500, log P_{OW} < -1 to >4	5
MW > 500, log P_{OW} -1 to 4	5
MW < 500, log P_{OW} -1 to 4	2
Orally exposed substances like lipsticks, toothpaste, mouthwash or used under occlusive conditions (deodorants)	1

Suggested Steps for application of the TTC approach to cosmetic ingredients and impurities:

- **Define product type, its intended use and related skin surface area involved.**
- **Define concentration of ingredient in the product.**
- **Estimate external exposure per day**
- **Estimate skin absorption of the ingredient based on ist physical and chemical characteristics**
- **If a rinse off product apply retention factor**
- **Establish use pattern: e.g. daily or intermittent use, if the latter is the case apply the default factor related to the use interval**
- **Calculate adjusted internal exposure per person per day (long-term average internal dosage for a 60 kg person).**
- **Where relevant, calculate total (aggregate) exposure when several cosmetic products contain this target ingredient**
- **Use this average aggregate internal dosage in the TTC decision tree of Kroes et al 2004**

Critique:

Of the 15,000 compounds listed in the Inventory of Cosmetic Ingredients only 155 have been characterised by Cramer et al.: An adequate update of the data base is needed.

The TTC approach only relates to systemic effects, local effects such as contact allergies, irritation, phototoxicity are not considered (because specific evaluation is necessary).

Genotoxic and carcinogenic compounds are not considered (although the approach can be easily adapted).

<u>However:</u>

The approach seems to be suitable to evaluate HH effects of dermal exposure of chemicals.

Adjustment to inhalation exposure is under way (OSIRS, ECETOC/CEFIC: Fraunhofer Institute).

Conclusion

TTCs can be used with other data to perform safety evaluation

TTCs have the potential to avoid animal testing

TTCs require reliable intake data and sufficient understanding of structural alerts

The Cramer evaluation of structural alerts needs to be updated to include more groups of compounds

TTCs are designed for oral exposure but can be adapted to dermal and inhalation exposure by evaluating NOELs of inhalation and dermal studies

References

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