UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI SCIENZE FARMACOLOGICHE E BIOTECNOLOGICHE

THE MOST UPDATED KNOWLEWDGE ON TTC

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UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI SCIENZE FARMACOLOGICHE

毒性学的懸念の閾値(TTC)に関する最新の知見

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食品安全委員会セミナー
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食品安全委員会事務局　仮訳

SUMMARY

- Why the TTC tool in risk characterization
- History
- Case studies:
  - flavourings
  - drug impurities
  - cosmetics
  - mixtures
  - unknown substances found in analysis of foods

要約

- リスク判定に毒性学的懸念の閾値(TTC)を使う理由
- 歴史
- 事例研究:
  - 香料
  - 医薬品中の不純物
  - 化粧品
  - 混合物
  - 食品分析で検出された未知の物質

RISK CHARACTERIZATION PARADIGM

✓ **Hazard identification**

- ❖ Inherent biological activity,

✓ **Hazard assessment**

- ❖ Dose-response analysis
- ❖ Assessment of relevance for humans

EXPOSURE ASSESSMENT
- ❖ Active principle
  - ❖ Dose of toxicant
  - ❖ Dose in individuals
  - ❖ Dose in special population groups
  - ❖ Max/min, chronically/occasionally

HAZARD IDENTIFICATION
- ❖ Identification of adverse health effects
  - ❖ Animal-based toxicological studies
  - ❖ *In vitro* toxicology data
  - ❖ In silico models (i.e.QSAR, comp.tox)
  - ❖ Human data

HAZARD ASSESSMENT
- ❖Quantification of adverse health effects
  - ❖ Dose-response for critical effect
  - ❖ Selection of critical data
  - ❖ Mode/mechanism of action
  - ❖ Kinetic variability
  - ❖ Dynamic variability

RISK CHARACTERISATION

リスク判定

✓ **ハザード同定**

- ❖ 固有の生物活性、

✓ **ハザード評価**

- ❖ 用量反応解析
- ❖ ヒトとの関連性の評価

暴露評価
- ❖ 有効成分
  - ❖ 毒性物質用量
  - ❖ 1人当たりの用量
  - ❖ 特定の人口集団における用量
  - ❖ 最大/最少，常時の/不定期の

ハザード同定
- ❖ 健康上の有害事象の同定
  - ❖ 動物を用いた毒性試験
  - ❖ *In vitro* の毒性データ
  - ❖ 構造活性の考慮
  - ❖ ヒトのデータ

ハザード評価
- ❖ 健康上の有害事象の定量化
  - ❖ 最小影響を示す用量反応相関
  - ❖ 重要なデータの選別
  - ❖ 作用機序
  - ❖ 動態変化
  - ❖ 動的変化

リスク判定

THRESHOLD OF TOXICOLOGICAL CONCERN AND THE RISK CHARACTERIZATION PARADIGM

- **Hazard identification**
  - ❖ **Inherent biological activity,**
- **Hazard characterisation**
  - ❖ **Dose-response analysis**
  - ❖ **Assessment of relevance for humans**

EXPOSURE ASSESSMENT
- ❖ Levels of substance in food and diet
- ❖ Amounts of food consumed
- ❖ Intake in special population groups
- ❖ Intake in individuals
  - ❖Max/min, regularly/occasionally

HAZARD IDENTIFICATION
- ❖ Identification … adverse … lth effects
  - ❖ Huma … data
  - ❖ Animal-b … ogical studies
  - ❖ *In vitro* … ata
  - ❖ Struc … ideration

HAZARD CHARACTERISATION
- ❖Quantification … adverse … lth effects
  - ❖ Dose … ical effect
  - ❖ Selecti … data
  - ❖ Mode/m … f action
  - ❖ Kinet …
  - ❖ Dynam … riabil …

RISK CHARACTERISATION

リスク判定のパラダイムの（を用いた）基準

- **ハザード同定**
  - ❖ **固有の生物活性、**
- **ハザード判定**
  - ❖ 用量反応解析
  - ❖ ヒトとの関連性の評価

暴露評価
- ❖ **有効成分**
  - ❖ **毒性物質用量**
  - ❖ **1人当たりの用量**
  - ❖ **特定の人口集団における用量**
  - ❖ **最大/最少，常時の/不定期の**

ハザード同定
- ❖ **健康上の有害事 … の同定**
  - ❖ **動物 …**
  - ❖ ***In vitro* …**
  - ❖ **構造活性 …**
  - ❖ **ヒトの …**

ハザード評価
- ❖ **健康上の有害 … の定量化**
  - ❖ **最小 … 相関**
  - ❖ **重要な …**
  - ❖ **作用機序 …**
  - ❖ **動態 …**
  - ❖ **動的 …**

リスク判定

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC) IN RISK CHARACTERISATION

The threshold of toxicological concern (TTC)

is a pragmatic risk assessment tool that is based on the principle of:

establishing a human exposure threshold value for all chemicals so low
that "risk assessment" could be based on
structural considerations alone
and toxicological specific data are not required

リスク判定における毒性学的懸念の閾値 (TTC)

毒性学的懸念の閾値 (TTC)

は実用的なリスク評価ツールで、次の点をベースにしている:

すべての化学物質に対するヒトの暴露閾値を低く設定しているので、
"リスク評価" は化学構造のみを考慮に入れることに基づいて行うことができ、
毒性学に特化したデータは必要とされていない

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- Suggested for risk prioritization of **trace chemicals in food**. *(2011)*

TTCの適用

- **容器包装材から移行した物質 (USFDA-TOR- 1993)**
- 食品中の**香料物質** (WHO-JECFA 1993,1995,1999….)
- 化学物質のリスク評価への適用への提案 (WHO-IPCS 1998)
- 地下水中の**植物保護剤の代謝産物**と無関係なもの (EC-2002)
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- 地表水中で検出される可能性のある**混合物**への提案 (2011)
- 食品に含まれる**検出限界以下の化学物質**のリスクの優先順位づけへの提案 (2011)

THRESHOLD OF REGULATION (TOR) APPROACH FOR FOOD CONTACT MATERIALS

- Dietary concentration of chemicals, without structural alerts for carcinogenicity, below 0.5 ppb (500 ng/kg or 500ng/L), is so negligible that it presents no public health concern (USFDA):

  a daily exposure level of 1.5 µg/person/day was derived
  assuming that a person consumes 1500 g of food and 1500 g of fluids daily
  and the chemical is distributed evenly throughout the total diet

  Food contact materials with an exposure below this level are "Exempted from regulation".

- TTC principle is derived from FDA's Threshold of Regulation (TOR) approach for food contact materials.

(Cheeseman et al, 1999)

規制上の閾値 (TOR)
食品接触材へのアプローチ

- 食べ物の中の化学物質（発がん性が疑われる構造を持つものを除く）の濃度が 0.5 ppb（500 ng/kg または 500ng/L）であれば無視できるので、健康への懸念はない：

  ヒト1人が1日に 1500gの食品と1500gのフルーツを食べ、化学物質が食べ物全体に
  均一に分布していると仮定すると、毎日の暴露量は1.5 µg/人/日ということになる
  このレベル以下の暴露量の食品接触材は、"規制の対象外"となる

- TTCの原則は、食品接触材へのFDAの規制上の域値 (TOR) アプローチから派生したものである

(Cheeseman et al., 1999)

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC)

THRESHOLD IN RELATION TO STRUCTURAL CLASSES Refinement by Munro *et al.* (1996)

- The Threshold of Regulation(TOR) value was based on a carcinogenicity database (FDA 1995)
- Munro and coworkers (1996) evaluated the use of TTC related to other endpoints than carcinogenicity (612 compounds)
- They used structural information based on an algorithm developed in 1978 by Cramer *et al.*
- The chemicals were grouped into three structural classes based on a "decision tree" approach.

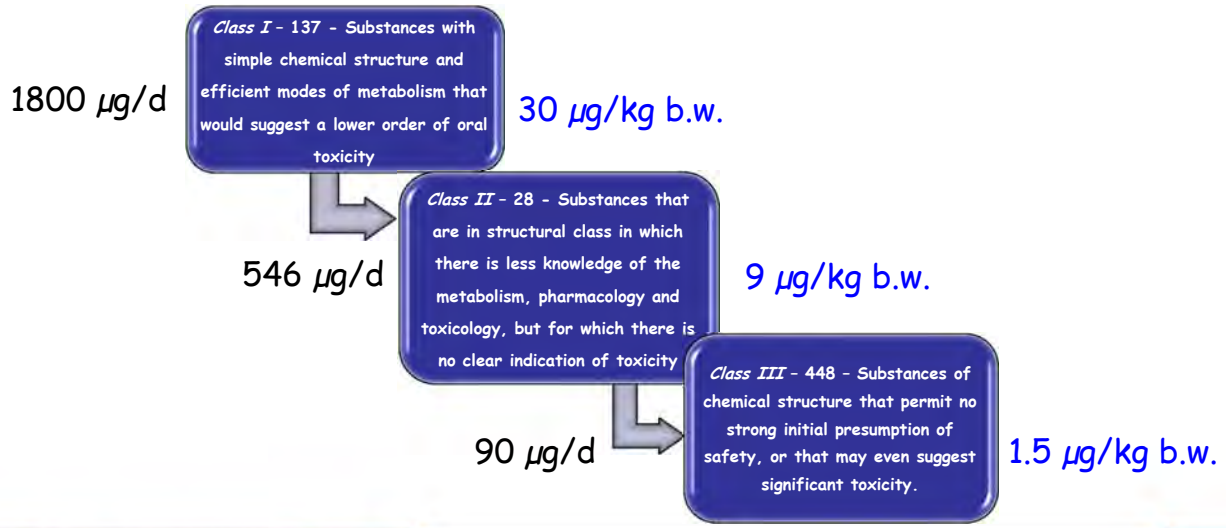
毒性学的懸念の閾値 (TTC)

化学構造クラスと関連する閾値 Munro らによる改良 (1996)

- 規制上の閾値(TOR) は発がん性データベースを基にしたもの (FDA 1995)
- Munro とその共同研究者ら (1996) は、612種類の化合物について、発がん性以外のエンドポイントが使われているか調べた
- Munroらは、その調査に、Cramerらが1978年に開発したアルゴリズムをもとにした化学構造の情報を用いた
- 612種類の化合物は、ディシジョンツリーに基づいて3つの化学構造クラスに分類された

CRAMER CLASSIFICATION TREE

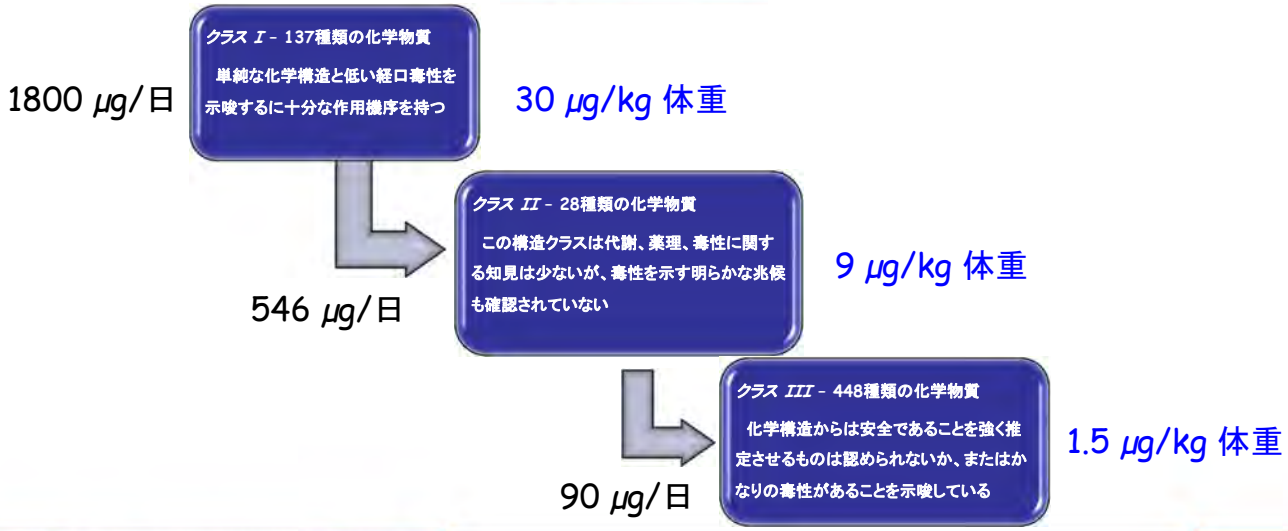
TTC EXPOSURE LIMITS



Munro et al., 1996

CRAMERによる分類ツリー

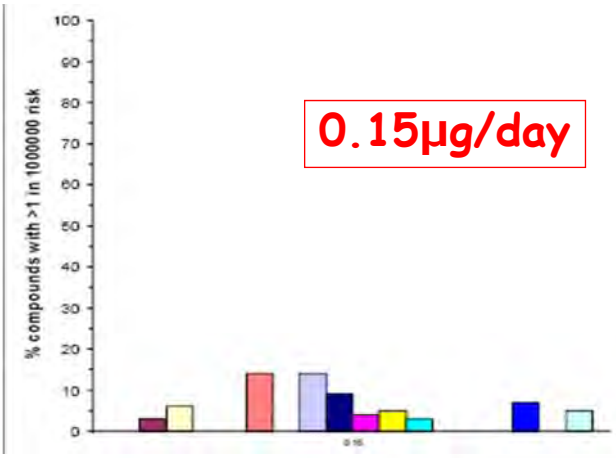
TTC暴露限界



Munro et al., 1996

CARCINOGENS WITH STRUCTURAL ALERT FOR GENOTOXICTY

Upper bound risk for cancer lower than one in a million? (calculated by linear extrapolation from the TD50)



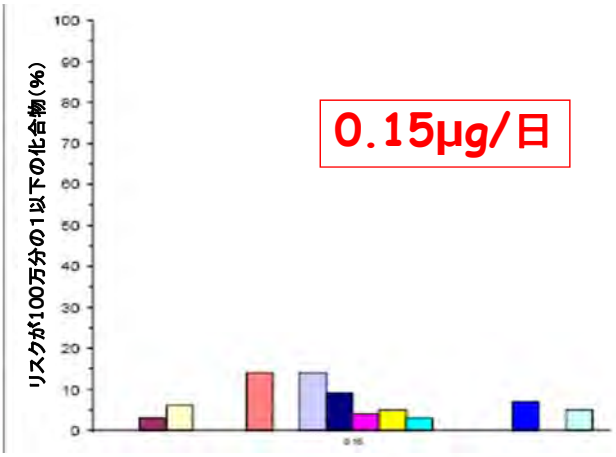
0.15µg/day

- Recommendation of using a TTC of 0.15 µg/day for substances with structural alerts for genotoxicity

Kroes et al. (2004)

遺伝毒性を疑わせる構造的特徴を持った発がん性物質

発がんが100万人に1人以下の場合のリスクの上限は？ (直線外挿法を用いてTD50から計算)



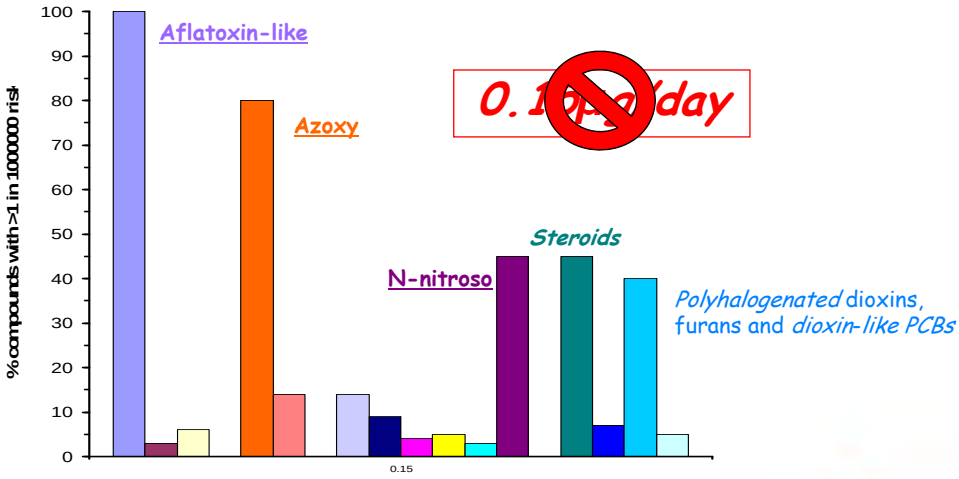
0.15µg/日

- 遺伝毒性を疑わせる構造的特徴を持った化合物では、0.15 µg/日のTTCを適用することを提言

Kroes et al. (2004)

COHORT OF CONCERN

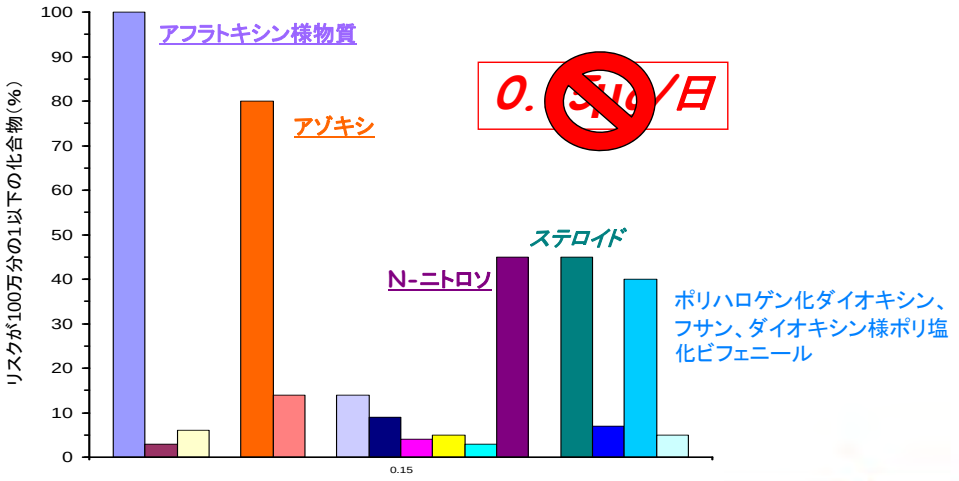
Upper bound risk for cancer lower than one in a million? (calculated by linear extrapolation from the TD50)



Kroes et al. (2004)

コホート別の懸念

発がんが100万人に1人以下の場合のリスクの上限は？ (直線外挿法を用いてTD50値から計算)



Kroes et al. (2004)

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC) IN RISK CHARACTERISATION

a TTC should NOT be considered.

- For specific structural alerts: i.e. **aflatoxin-like**, **azoxy** and **N-nitroso**-compounds (potent genotoxic carcinogens)
- **Polyhalogenated dibenzo-p-dioxins, -dibenzofurans and dioxin like PCB's** (non-genotoxic carcinogens, bioaccumulative, with very large kinetic differences between animals and humans)
- **Steroids** (potent non-genotoxic carcinogens)

- **Non essentials metals and metal containing compounds** (not included in the data base)
- **Proteins** (risk of allergenicity, not included in database)
- **High molecular weight chemicals such as polymers** (not included in database)
- **Nanomaterials** (not included in database)

Kroes et al. (2004)

リスク判定における毒性学的懸念の閾値（TTC）

TTCは考慮されるべきではない

- 遺伝毒性を疑わせる特殊な構造的特徴： アフラトキシン様構造、アゾキシ基、Nニトロソ基を持つ化合物など（発がん作用の強い物質）
- ポリ塩化ジベンゾ−パラ−ジオキシン、ポリ塩化ジベンゾフラン、およびジオキシン様PDB （動物-ヒト間の非常に大きな動態の違いを伴った非遺伝毒性発がん物質、生体内蓄積）
- ステロイド（非遺伝性発がん作用の強い物質）

- 非必須金属および金属含有化合物 （データベースには含まれていない）
- タンパク質 （アレルゲン性、データベースには含まれていない）
- ポリマー等の高分子化合物 （データベースには含まれていない）

Kroes et al. (2004)

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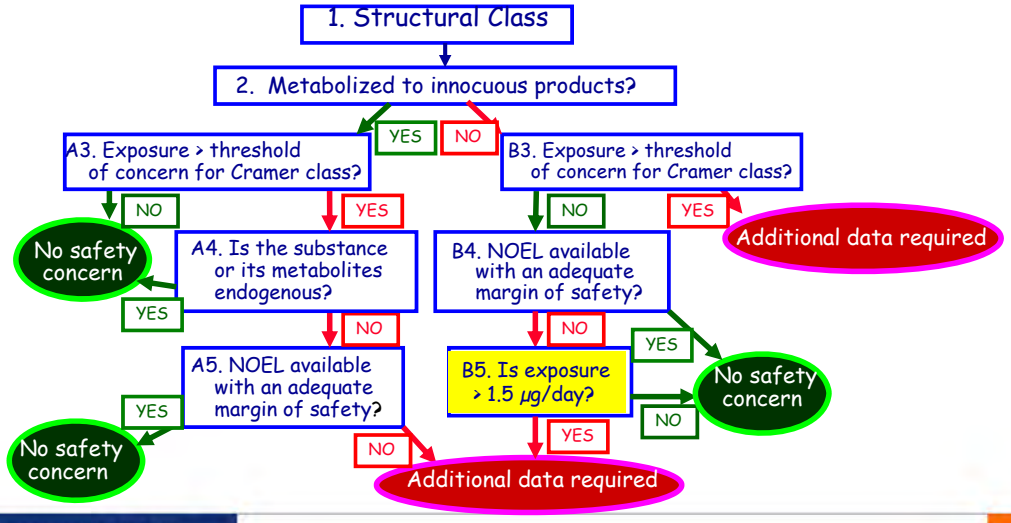
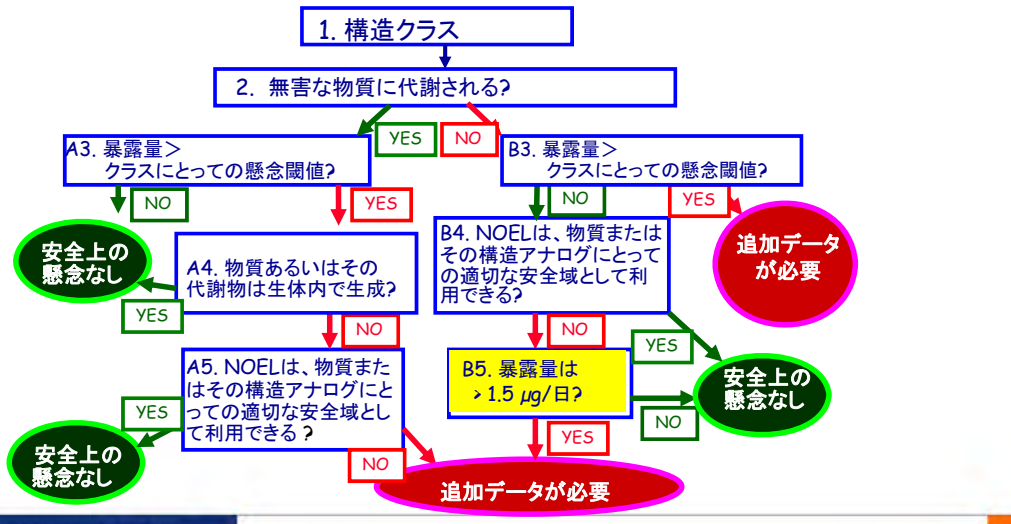
JECFA* - FLAVOURINGS SAFETY ASSESSMENT



*The Joint FAO/WHO Expert Committee on Food Additives (JECFA)

JECFA* - 香料物質の安全性評価



* FAO/WHO合同食品添加物専門家会議

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GENOTOXIC IMPURITIES IN PHARMACEUTICAL PREPARATIONS

		DURATION OF EXPOSURE				
		≤ 1 month	1 – 3 months	3 - 6 months	6 – 12 months	> 12 months
Muller et al. (2006) Daily Intake (µg/day)	Not listed	120	40	20	10	1.5
EMA (2008) Daily Intake (µg/day)	Single 120	60	20	10	5	1.5
FDA (2008) Daily Intake (µg/day)	<14 days 120	60	20	10	5	1.5

10^{-6} cancer risk – extra conservatism during shorter duration trials (e.g. for volunteers)

10^{-5} cancer risk – risk used by ICH for carcinogenic residual solvents and CHMP draft for genotoxic impurities

医薬品中の遺伝毒性のある不純物

		暴露期間				
		≤ 1か月	1 – 3 か月	3 – 6 か月	6 – 12か月	> 12か月
Muller et al. (2006) 一日摂取量 (µg/day)	未記載	120	40	20	10	1.5
EMA (2008) 一日摂取量 (µg/day)	単回投与 120	60	20	10	5	1.5
FDA (2008) 一日摂取量 (µg/day)	<14日間 120	60	20	10	5	1.5

10^{-6} の発がんリスク – 比較的短期の試験（ボランティアによる試験など）に見られる、過度に安全側に立った考え方）

10^{-5} の発がんリスク – 日米EU医薬品規制調和国際会議（ICH）のがん原生残留物基準および欧州医薬品庁のヒト用医薬品委員会（CHMP）の遺伝毒性不純物基準案を用いたリスク

TTC APPLICATIONS

- **Migrant** substances from packaging materials (USFDA-TOR- 1993)
- **Flavourings** substances in food (WHO-JECFA 1993,1995,1999….)
- Endorsed for the risk assessment of chemicals (WHO-IPCS 1998)
- Non relevant **plant protection product metabolites** in ground water (EC-2002)
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- Impurities, breakdown and reaction products, metabolites and low level contaminants in food and feed. (**EFSA** 2102)

- Suggested for application to **aquatic environmental** exposure (2005)
- **SUGGESTED FOR APPLICATION TO THE COSMETIC INGREDIENTS AND THEIR IMPURITIES (2007)**
- Suggested for **prenatal developmental** toxicity (2010)
- Suggested for **mixture of substances** potentially detectable in surface water (2011)
- Suggested for risk prioritization of **trace chemicals in food**. *(2011)*

TTCの適用

- 容器包装材から**移行した**物質 (USFDA-TOR- 1993)
- 食品中の**香料物質** (WHO-JECFA 1993,1995,1999….)
- 化学物質のリスク評価への適用への提案 (WHO-IPCS 1998)
- 地下水中の**植物保護剤の代謝産物**と無関係なもの (EC-2002)
- 医薬品中の遺伝毒性のある不純物 (EMA 2003,2004)
- 食品中の**香料物質** (EFSA 2004)
- 漢方薬中の遺伝毒性のある構成成分 (EMA 2006)
- **REACH** (化学物質の登録、評価、認可および制限に関する規則) に対する提案 (ECHA 2008)

- **水環境**中での暴露への適用に対する提案 (2005)
- **化粧品成分およびその不純物への適用に対する提案（2007)**
- **出生前発生**毒性に対する提案 (2010)
- 地表水中で検出される可能性のある**混合物**への提案 (2011)
- 食品に含まれる**微量化学物質**のリスクの優先順位づけへの提案 (2011)

APPLICATION OF THE TTC TO COSMETIC INGREDIENTS


Michael Gibney, Dublin, EIR


Corrado Galli, Milano, I


Andy Renwick, Southampton, UK


Richard Guy, Bath, UK


Robert Kroes, Utrecht, NL


Helmut Greim, Munich, D


Victor Feron, Zeist, NL


Jean-Claude Lhuguneot, Dijon, F


J.M. van de Sandt, Zeist, NL

Kroes et al. FCT 2007

化粧品成分へのTTCの適用


Michael Gibney, Dublin, EIR


Corrado Galli, Milano, I


Andy Renwick, Southampton, UK


Richard Guy, Bath, UK


Robert Kroes, Utrecht, NL


Helmut Greim, Munich, D


Victor Feron, Zeist, NL


Jean-Claude Lhuguneot, Dijon, F


J.M. van de Sandt, Zeist, NL

Kroes et al. FCT 2007

I. SIMILARITY TO COMPOUNDS IN MUNRO ET AL. (1996) DATABASE ?

Fragrance ingredients	YES
Dyes and colourants	YES
Food-type components	YES
Low molecular weight organic compounds with various uses	YES
Normal organic constituents of the human body	YES
Pharmaceutical-type compounds	YES
Surfactants, emollients, humectants and emulsifying agents	YES
Plant and animal extracts	NO
Polymeric compounds (YES-monomers)	(NO)
Inorganic salts of various metals	(NO)

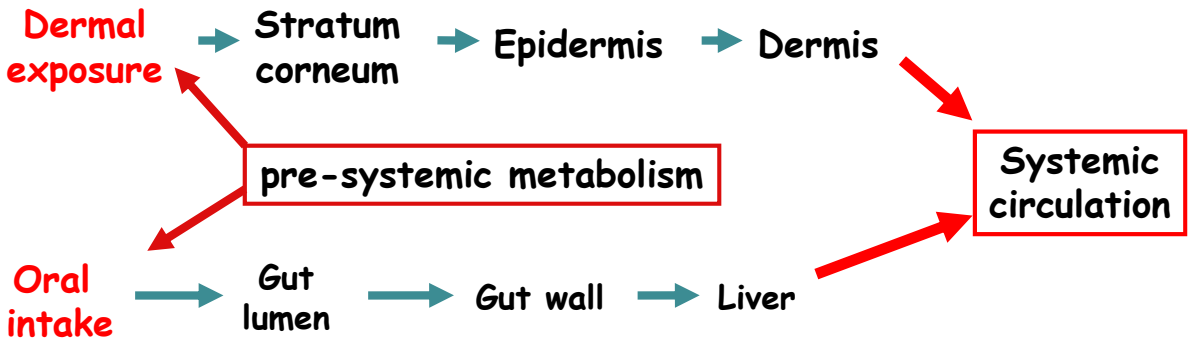
Kroes et al. FCT 2007

I．MUNROらのデータベース(1996) における化合物の類似点

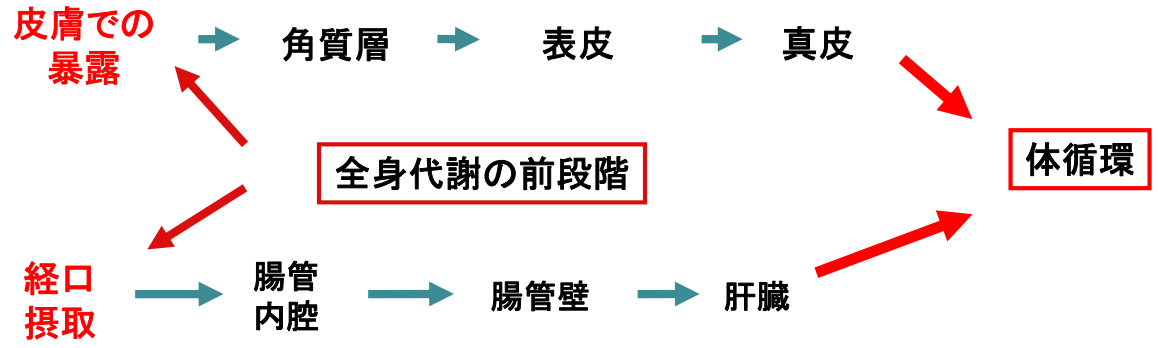
芳香成分	YES
染料および顔料	YES
食物成分	YES
多用途の低分子有機化合物	YES
人体の通常の有機成分	YES
医薬品成分	YES
界面活性剤、柔軟剤、保湿剤、乳化剤	YES
植物および動物の抽出物	NO
高分子化合物 (YES-モノマー)	NO
さまざまな金属の無機塩	NO

Kroes et al. FCT 2007

II. COULD TOPICAL APPLICATION AFFECT THE ABSORBED FRACTION THAT IS CONVERTED TO INACTIVE OR TOXIC METABOLITES COMPARED TO ORAL ADMINISTRATION ?



Ⅱ. 皮膚への塗布は、経口摂取と比較した場合、不活性あるいは毒性のある代謝物に変化する物質の吸収率に影響を与えたか?



THERE ARE TWO TOXICOLOGICALLY RELEVANT SCENARIOS

Extensive presystemic metabolism via the oral route

- if the parent compound were the active form and first-pass metabolism of the oral dose resulted in detoxication, the oral toxicity database of Munro et al. (1996) could under-predict toxicity after topical application.

- if the presystemic metabolite were the active form and first-pass metabolism of the oral dose resulted in bioactivation, the oral toxicity database of Munro et al. (1996) could over-predict toxicity after topical application.

Kroes et al. FCT 2007

毒性学的に関連する2つのシナリオ

経口経路を介した、広範囲に及ぶ全身循環以前の代謝

- もしも親化合物が活性体であり、経口摂取された物質の初回通過代謝により解毒されるならば、Munroらの毒性データベース(1996)は皮膚塗布後の毒性を過小評価する可能性がある

- もしも全身循環以前の代謝物が活性体であり、経口摂取された物質の初回通過代謝により生体内で活性化されるならば、Munroらの毒性データベース(1996)は皮膚塗布後の毒性を過大評価する可能性がある

Kroes et al. FCT 2007

III. EXPOSURE ?

- Can the extent of systemic uptake be modelled using the compound's physicochemical properties?
- Can different exposure scenarios be allowed for by realistic uptake adjustment factors?

Kroes et al. FCT 2007

Ⅲ. 暴露？

- 化合物の物理化学的特性を利用して、全身からの吸収の程度をモデル化することは可能か?
- 現実の摂取量に調整するための係数を使うことで、異なった暴露シナリオの設定は可能か?

Kroes et al. FCT 2007

THE MAXIMUM FLUX ACROSS THE SKIN

(Jmax in μg/cm²/hour)

Jmax can be related to the permeability coefficient Kp (cm/h) and the saturation solubility in the water

$$J_{max} = K_p * C^{sat}_{water}$$

Estimated experimentally

$$\log K_p = -2.7 + 0.71 * \log P - 0.0061 * MW$$

P = octanol-water partition coefficient of the chemical - MW = molecular weight

Kroes et al. FCT 2007

皮膚を透過する物質溶液の最大流量

(Jmax in μg/cm²/hour)

Jmaxは、溶液の透過係数 Kp（cm/時）および飽和溶解度と関連している

$$J_{max} = K_p * C^{sat}_{water}$$

実験的に評価された

$$\log K_p = -2.7 + 0.71 * \log P - 0.0061 * 分子量$$

P = オクタノール-水の分配係数

Kroes et al. FCT 2007

PROPOSED DEFAULT ADJUSTMENT FACTORS FOR THE % DOSE ABSORBED OF COSMETIC INGREDIENT ACROSS THE SKIN

Jmax ($\mu g/cm^2/hr$) (maximum flux across the skin for that chemical)	Default % Dose Absorbed (24 hrs)
Non-reactive chemicals above 1000 Dalton	Negligible
Jmax < 0.1	10%
$0.1 < J_{MAX} < 1.0$	40%
Jmax > 10	80%

Kroes et al. FCT 2007

化粧品成分の経皮吸収量%を算定するための調整係数既定値の提案

Jmax ($\mu g/cm^2$/時) （皮膚を透過する物質の最大流量）	吸収量の既定値%(24時間)
1000ダルトン超の非反応性化学物質	無視できるほど微量
Jmax < 0.1	10%
$0.1 < J_{MAX} < 1.0$	40%
Jmax > 10	80%

Kroes et al. FCT 2007

TTC ANALYSIS OF KNOWN CALENDULA (Dry Petal) CONSTITUENTS WITH KNOWN %

	CAS number	(ToxTree)	Molecular Weight	Calculated Log KOW	Estimated Jmax	Default % Absorption	Systemic Exposure (ug/day)1
FLAVONOIDS <1.5%							
astragalin	480-10-4	3 (90 ug/day)	448,378	0.49 ± -1.11			
hyperoside	482-36-0	3 (90 ug/day)	464,377	0.30 ± -1.34			
isoquercitrin	21637-25-2	3 (90 ug/day)	464	-0,1	Jmax <0.1	10	<27
isorhamnetin	480-19-3	3 (90 ug/day)	316,264	2.39 ± 0.54	Jmax <0.1	10	<27
kaempferol	520-18-3	3 (90 ug/day)	286	1,96	0.1 <J max <10	40	<108*
neohesperidin (Closest Match to Neoliesperoside)	13241-33-3	3 (90 ug/day)	610,562	-0.05 ± 1.60	Jmax <0.1	10	<27
narcissin	604-80-8	3 (90 ug/day)	624,545	-0.45 ± 1.35	Jmax <0.1	10	<27
quercetin	117-39-5	3 (90 ug/day)	302,237	1,48	0.1 <Jmax <10	40	<108*
rutin	153-18-4	3 (90 ug/day)	610.518.	-2,02	Jmax <0.1	10	<27
syringenin (Closest Match to Syringentin)	118-34-3	3 (90 ug/day)	372,368	-0.45 ± 1.35	Jmax <0.1	10	<27
typhaneoside	104472-68-6	3 (90 ug/day)	770,686	7.57 ± 1.23	Jmax <0.1	10	<27
TANNINS 6 - 10%							
pyrogallol	87-66-1	1 (1800 ug/day)	126,11	0,97	Jmax >10	80	1440
catechol	120-80-9	1 (1800 ug/day)	110,111	0,88	Jmax >10	80	1440
FREE & ESTERIFIED TRITERPENIC ALCOHOLS <5%							
arnidiol	6750-30-7	1 (1800 ug/day)	442,723	7.57 ± 1.23	Jmax <0.1	10	<90
calenduladiol	10070-48-1	1 (1800 ug/day)	442,723	7.65 ± 1.17	Jmax <0.1	10	<90
erythrodiol	545-48-2	1 (1800 ug/day)	442,723	7.71 ± 0.76	Jmax <0.1	10	<90
faradiol	20554-95-4	1 (1800 ug/day)	442,723	7.53 ± 0.87	Jmax <0.1	10	<90
longispinogenin	465-94-1	3 (90 ug/day)	472,7488	6.91 ± 0.76	Jmax <0.1	10	<90
lupeol	545-47-1	1 (1800 ug/day)	426,724	9,23	Jmax <0.1	10	<90
maniladiol	595-17-5	1 (1800 ug/day)	442,723	7.55 ± 0.62	Jmax <0.1	10	<90
pseudotaraxasterol or psi-Taroxosterol	464-98-2	1 (1800 ug/day)	426,724	8.91 ± 1.31	Jmax <0.1	10	<90
taraxasterol	1059-14-9	1 (1800 ug/day)	426,724	8.69 ± 1.46	Jmax <0.1	10	<90
ursodiol	128-13-2	3 (90 ug/day)	392,576	3,00	?		
alpha-amyrin	638-95-9	1 (1800 ug/day)	426,724	9,16	Jmax <0.1	10	<90
TRITERPENIC GLYCOSIDES 2 - 10%							
calenduloside B (8CI)	34381-98-1	3 (90 ug/day)	943,126	2.49 ± 2.46			

1- Based upon full body application of 18 g of formulas/day, 0.1% concentration of dry petal, and UNITIS concentration of the chemical in the extract.

Application of the threshold of toxicological concern approach for the safety evaluation of calendula flower (Calendula officinalis) petals and extracts used in cosmetic and personal care products.
Re TA, Mooney D, Antignac E, Dufour E, Bark I, Srinivasan V, Nohynek G. Food Chem Toxicol. 2009 Jun;47(6):1246-54

既知の%を用いたカレンデュラ(キク科植物)(乾燥花弁)の成分分析

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UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI FARMACIA

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- Suggested for application to the **cosmetic ingredients** and their impurities (2007)
- Suggested for **prenatal developmental** toxicity (2010)
- **SUGGESTED FOR MIXTURE OF SUBSTANCES POTENTIALLY DETECTABLE IN SURFACE WATER (2011)**
- Suggested for risk prioritization of **trace chemicals in food**. *(2011)*

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- 漢方薬中の遺伝毒性のある構成成分 (EMA 2006)
- **REACH** (化学物質の登録、評価、認可および制限に関する規則) に対する提案 (ECHA 2008)

- **水環境**中での暴露への適用に対する提案 (2005)
- 化粧品成分およびその不純物への適用に関する提案 (2007)
- **出生前発生**毒性に対する提案 (2010)
- **地表水中で検出される可能性のある混合物への提案 (2011)**
- 食品に含まれる**検出限界以下の化学物質**のリスクの優先順位づけへの提案 (2011)

TIER 0 – SUBSTANCES POTENTIALLY DETECTABLE IN SURFACE WATER

- **10 COMPOUNDS** detected in surface water, were classified into Cramer Classes, assuming that no toxicological information, other than structure, is available,
- **TTC values** for each substance assigned
  Cramer Class I (1800 µg/day = 0.0300 mg/kg b.w. day)
  Cramer Class II (540 µg/day = 0.0091 mg/kg b.w. day)
  Cramer Class III (90 µg/day = 0.0015 mg/kg b.w.day)
- **Exposure** (mg/kg b.w. day) = Surface water concentration (mg/L) x 0.42 L day/18 Kg (children)
  (Drinking water assumption made for children to be conservative)
- **Hazard Quotient (HQ)** for each substance = Exposure/TTC value

事例研究 A:
階層 0 –地表水から検出される可能性のある物質

- 地表水から検出される可能性のある10種類の化合物は、化学構造以外の毒性学的情報はないと仮定して、Cramerのクラスに分類された
- 各物質のTTC値は以下のように割り当てられた
  Cramer クラス I (1800 µg/日 = 0.0300 mg/kg 体重/日)
  Cramer クラス II (540 µg/日 = 0.0091 mg/kg 体重/日)
  Cramer クラス III (90 µg/日 = 0.0015 mg/kg 体重/日)
- 暴露量 (mg/kg 体重/日) =
  地表水濃度 (mg/L) x 0.42 L 日/18 Kg (小児)
  (飲料水の暴露量予測は、小児において、より安全側に立ったものになった)
- 各物質のハザード比（HQ）=
  暴露量/TTC値

TIER 0 – SUBSTANCES POTENTIALLY DETECTABLE IN SURFACE WATER

COMPOUND	EXPOSURE (mg/kg-bw/day)	TTC VALUE (mg/day)	TTC VALUE (mg/kg-bw/day)	HAZARD QUOTIENT (HQ) BASED ON TTC
A	1.94E-06	0.546	0.0091	2.1E-04
B	1.77E-06	0.090	0.0015	1.2E-03
C	8.87E-05	0.546	0.0091	9.7E-03
D	3.97E-05	1.800	0.0300	1.3E-03
E	3.03E-06	0.090	0.0015	2.0E-03
F	4.20E-06	0.090	0.0015	2.8E-03
G	7.93E-04	0.546	0.0091	8.7E-02
H	6.53E-06	1.800	0.0300	2.2E-04
I	1.42E-04	0.090	0.0015	9.5E-02
J	2.57E-05	1.800	0.0300	8.6E-04
HAZARD INDEX				0.2

The calculated **Hazard Index of 0.2 is less than 1.0**, and therefore the results of this Tier 0 assessment would suggest that advancement to higher assessment tiers is not necessary in this case.

事例研究 A:
階層 0 –地表水から検出される可能性のある物質

化合物	暴露量 (mg/kg体重/日)	TTC値 (mg/日)	TTC値 (mg/kg体重/日)	TTCに基づくハザード比 (HQ)
A	1.94E-06	0.546	0.0091	2.1E-04
B	1.77E-06	0.090	0.0015	1.2E-03
C	8.87E-05	0.546	0.0091	9.7E-03
D	3.97E-05	1.800	0.0300	1.3E-03
E	3.03E-06	0.090	0.0015	2.0E-03
F	4.20E-06	0.090	0.0015	2.8E-03
G	7.93E-04	0.546	0.0091	8.7E-02
H	6.53E-06	1.800	0.0300	2.2E-04
I	1.42E-04	0.090	0.0015	9.5E-02
J	2.57E-05	1.800	0.0300	8.6E-04
危険指数				0.200

算定された危険指数0.2 は1.0未満であり、この階層 0の評価結果は、この事例では より高次の評価をする必要がないことを示唆している

TTC APPLICATIONS

- **Migrant** substances from packaging materials (USFDA-TOR- 1993)
- **Flavourings** substances in food (WHO-JECFA 1993,1995,1999….)
- Endorsed for the risk assessment of chemicals (WHO-IPCS 1998)
- Non relevant **plant protection product metabolites** in ground water (EC-2002)
- **Genotoxic impurities** in pharmaceutical preparations (EMA 2003,2004)
- **Flavourings** substances in food (EFSA 2004)
- **Genotoxic constituents** in herbal preparations (EMA 2006)
- Suggested for **REACH** (**R**egistr, **E**valuat, **A**uthoriz and restrict of **Ch**emical substances) (ECHA 2008)
- Impurities, breakdown and reaction products, metabolites and low level contaminants in food and feed. (**EFSA** 2102)

- Suggested for application to **aquatic environmental** exposure (2005)
- Suggested for application to the **cosmetic ingredients** and their impurities (2007)
- Suggested for **prenatal developmental** toxicity (2010)
- Suggested for **mixture of substances** potentially detectable in surface water (2011)
- **SUGGESTED FOR RISK PRIORITIZATION OF TRACE CHEMICALS IN FOOD. *(2011)***

TTCの適用

- 容器包装材から**移行した**物質 (USFDA-TOR- 1993)
- 食品中の**香料物質** (WHO-JECFA 1993,1995,1999….)
- 化学物質のリスク評価への適用への提案 (WHO-IPCS 1998)
- 地下水中の**植物保護剤の代謝産物**と無関係なもの (EC-2002)
- 医薬品中の遺伝毒性のある不純物 (EMA 2003,2004)
- 食品中の**香料物質** (EFSA 2004)
- 漢方薬中の遺伝毒性のある構成成分 (EMA 2006)
- **REACH** (化学物質の登録、評価、認可および制限に関する規則) に対する提案 (ECHA 2008)

- **水環境**中での暴露への適用に対する提案 (2005)
- 化粧品成分およびその不純物への適用に関する提案 (2007)
- **出生前発生**毒性に対する提案 (2010)
- 地表水中で検出される可能性のある混合物への提案 (2011)
- **食品に含まれる微量化学物質のリスクの優先順位づけへの提案(2011)**

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Application of the TTC concept to unknown substances found in analysis of foods

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APPLICATION OF THE TTC CONCEPT TO UNEXPECTED PEAKS FOUND IN ANALYSIS OF FOODS AT TRACE LEVELS.

- During ***routine monitoring of a food*** in a quality control laboratory, an extra peak is detected.
- In the evaluation of ***a new processing technology*** (irradiation, a new heat-process, etc) a new peak was detected at trace level that are not present in the food being processed in traditional manner.
- An unknown peak occurs in the food due to the fact that a manufacturer intends to use a food contact material containing ***a novel raw material to package the food***..
- A manufacturer of an approved food additive has ***changed the production process*** slightly. A comparison of the existing additive and the new product shows a new peak that is not described in the specifications.

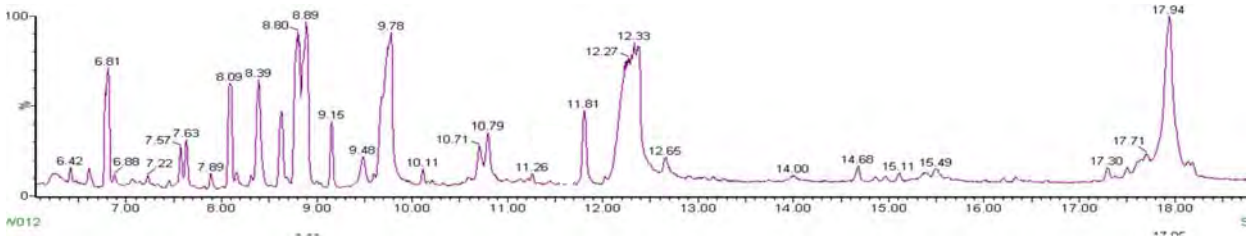
Are the unexpected peaks a health concern?

追跡レベルでの食品分析の中で検出される予期しないピークへのTTC概念の適用

- 品質管理室で**定型の食品モニタリング**において、LC-蛍光検出法によって、以前には認められなかった予期しない追加のピークが検出されている
- 新しい加工技術（X線照射、新しい熱加工など）の評価中に、従来の方法で加工されている食品中には存在しない一連の新しいピークが、追跡レベルで検出された
- 製造業者は、食品を包装するために、新しい原料を含んだ食品接触材を使おうとしている。食品には未知のピークが現れる
- 認可済みの食品添加物を製造している業者は、若干、**製造工程を変更した**。従来の添加物と新しい添加物の液体クロマトグラフ質量分析（LC-MS）を使った比較から、仕様書に記載されていないいくつかのわずかな違いが認められた。それらの差異には、新しいピークがわずかに含まれている

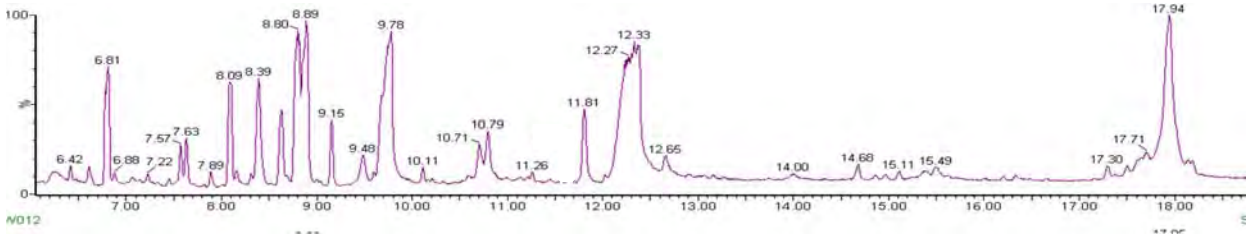
予期しないピークは健康上の懸念となるか？

EXAMPLES: CUCUMBER



pesticide screen of cucumber extracts by GC-MS

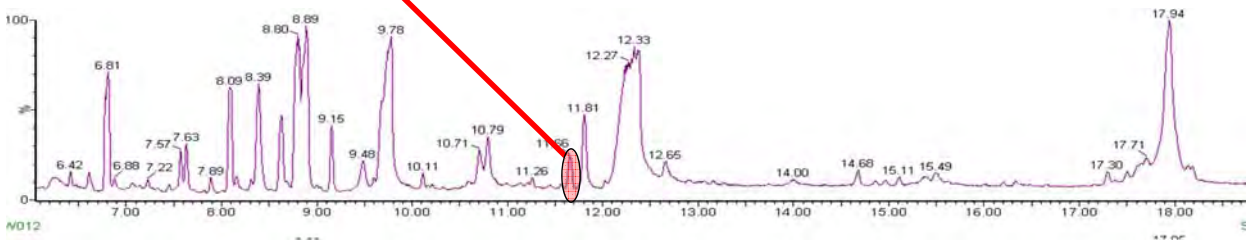
例： キュウリ



ガスクロマトグラフ質量分析によるキュウリ抽出物の農薬スクリーン

EXAMPLES: CUCUMBER

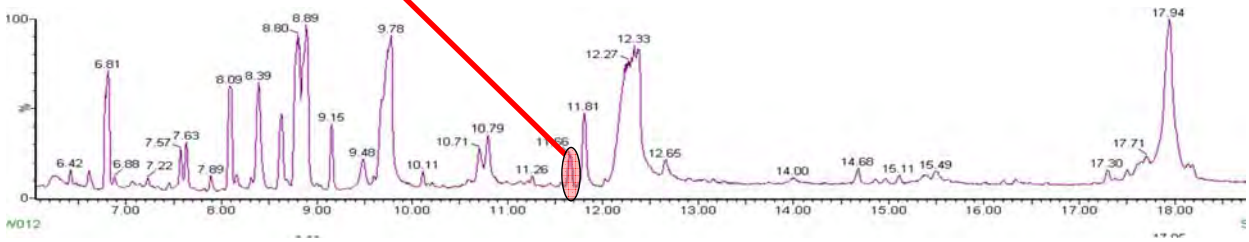
New peak was detected



pesticide screen of cucumber extracts by GC-MS

例： キュウリ

新たなピークが検出された



ガスクロマトグラフ質量分析によるキュウリ抽出物の農薬スクリーン

TTC EXCLUDED CLASSES:
CLASSES OF SUBSTANCES NOT COVERED BY TTC

Class/Group	Reason for exclusion
Aflatoxin-like compounds[1]	Potent genotoxic carcinogens
N-nitroso-compounds[1]	Potent genotoxic carcinogens
Azoxy-compounds[1]	Potent genotoxic carcinogens
Steroids[1]	Potent non-genotoxic carcinogens
Polyhalogenated dibenzo-p-dioxins, -dibenzofurans and dioxin like PCB's[1]	Bioaccumulative, non-genotoxic carcinogens, with very large kinetic differences between animals and humans
Proteins[2]	Risk of allergenicity, not included in database
(Non)-essential metals[2]	Not included in database, some are bioaccumulative
High molecular weight substances such as polymers[2]	Not included in database

[1]Cohort of Concern
[2]other 'TTC excluded classes

TTCはクラスを除外する:
TTCではカバーされない物質のクラス

クラス/グループ	除外理由
アフラトキシン様化合物[1]	強い遺伝毒性発がん性物質
N-ニトロソ化合物[1]	強い遺伝毒性発がん性物質
アゾキシ化合物[1]	強い遺伝毒性発がん性物質
ステロイド[1]	強い非遺伝毒性発がん性物質
ポリ塩化ジベンゾ-パラ-ジオキシン，ポリ塩化ジベンゾフランおよびジオキシン様PCB[1]	動物-ヒト間での非常に大きな動態上の差異を伴った、生物濃縮(or生体内蓄積)、非遺伝毒性発がん性物質
タンパク質[2]	データベースに含まれていないアレルギー誘発性のリスク
(非)必須金属[2]	データベースに含まれていない、生物濃縮(or生体内蓄積)するものもある
ポリマーのような高分子化合物[2]	データベースに含まれていない

[1]Cohort of Concern
[2]それ以外のTTC除外クラス

TIERED APPROACH:
PROPOSAL TO DEAL WITH UNKNOWN PEAKS

	Proposed tier	Background
Tier 1	Exclusion dependent on sample source	For some samples, it will be possible to exclude the presence of some or all 'TTC excluded classes' on basis of their origin.
Tier 2	Exclusion by chromatographic technique, sample preparation and/or detection method used or partial identification	Analytical techniques are relatively specific, so that a peak detected can only stem from a certain range of substances. They may also indicate the type of substance without providing a full identification.
Tier 3	Exclusion by targeted analysis	Analyses designed to detect certain structural elements can be applied.
Tier 4	Dietary exposure to food sources containing the unknown peak	Due to nutritional habits, exposure depends heavily on the food type.
Tier 5	Quantification of unknown compounds	For risk assessment, the concentration of the unknown peak in the sample has to be estimated with sufficient accuracy.

階層化アプローチ:
未知のピークに対応するための提案

	階層案	背景
階層 1	試料ソースによって決まる除外	いくつかの試料では、試料源をもとにいくつか、あるいはすべての 'TTC除外クラス' の存在を除外することができると思われる
Tier 2	Exclusion by chromatographic technique, sample preparation and/or detection method used or partial identification	Analytical techniques are relatively specific, so that a peak detected can only stem from a certain range of substances. They may also indicate the type of substance without providing a full identification.
Tier 3	Exclusion by targeted analysis	Analyses designed to detect certain structural elements can be applied.
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TIER 1
EXCLUSION DEPENDENT ON SAMPLE SOURCE

- Requires a complete knowledge of the product with all potential contaminants that may be present.
- What is source? Packaging? Transport? Storage? Processing?
- Use expert judgment to exclude specific toxic classes. For example:
  - Polypropylene-FCM unlikely to contain dioxins, aflatoxins etc.
  - If unidentified peak is off-flavour, non-essential elements, dioxins etc can be excluded because they are not volatile.

Based on expert judgement

階層 1
試料ソースによって決まる除外

- すべての高リスク汚染物質が混入している可能性のある製品に関するあらゆる知見が必要
- 試料ソースは? 包装は? 運搬は? 保存は? 加工は?
- 特定の毒性クラスを除外するために専門家の判断を活用する。 たとえば:
  - ダイオキシン類やアフラトキシン類等を含む可能性が低いポリプロピレン製食品接触材料
  - 未確認のピークが異臭原因物質、非必須元素、ダイオキシン類等であれば、それらは揮発性ではないので除外され得る

専門家の判断をもとにする

EXAMPLES: CUCUMBER

Tier 1 Exclusion by sample source

- Cucumber watery fruit. Negligible amounts of fat → **Dioxin like compounds** unlikely.
- **N-Nitroso compounds** are formed in the presence of nitrites and are more associated with processed foods than fresh fruit and vegetables and so are also excluded.
- **Azoxy compounds** are not typically associated with cucumber and therefore they were discounted at this stage

例： キュウリ

階層 1　試料源による除外

- キュウリ（水分が多い）。ごくわずかな脂肪 → **ジオキシン様化合物**の存在はほとんど考えられない
- **N-ニトロソ化合物**は亜硝酸化合物の存在下で合成されるもので、生の果物・野菜よりも加工食品に関係するものである。従って、除外される
- アゾキシ化合物はキュウリとは一般的に関係がなく、この段階では無視された

TIERED APPROACH:
PROPOSAL TO DEAL WITH UNKNOWN PEAKS

	Proposed tier	Background
Tier 1	Exclusion dependent on sample source	For some samples, it will be possible to exclude the presence of some or all 'TTC excluded classes' on basis of their origin.
Tier 2	Exclusion by chromatographic technique, sample preparation and/or detection method used or partial identification	Analytical techniques are relatively specific, so that a peak detected can only stem from a certain range of substances. They may also indicate the type of substance without providing a full identification.
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階層化アプローチ:
未知のピークに対応するための提案

	階層案	背景
Tier 1	Exclusion dependent on sample source	For some samples, it will be possible to exclude the presence of some or all 'TTC excluded classes' on basis of their origin.
階層 2	クロマトグラフィー技術、試料調製、および/または用いられた検出方法、または部分同定による除外	分析法は比較的特有のものなので、検出されたピークは物質の一定範囲で検出され得る。それらのピークは、また、完全同定しなくても物質のタイプを示唆する
Tier 3	Exclusion by targeted analysis	Analyses designed to detect certain structural elements can be applied.
Tier 4	Dietary exposure to food sources containing the unknown peak	Due to nutritional habits, exposure depends heavily on the food type.
Tier 5	Quantification of unknown compounds	For risk assessment, the concentration of the unknown peak in the sample has to be estimated with sufficient accuracy.

EXAMPLES: CUCUMBER

Tier 2 Analytical method (GPC and GC-MS)

- **Proteins and polymers** structure excluded by GPC
- **Steroids** require very high GC oven temperatures.
- **Aflatoxins** not volatile enough for GC analysis.
- MS library did not give (partial) identification.

例： キュウリ

階層 2 分析方法 (ゲル透過クロマトグラフィー および ガスクロマトグラフ質量分析法)

- ゲル透過クロマトグラフィーにより除外される**タンパク質およびポリマー**の構造
- **ステロイド**には、ガスクロマトグラフィーの際、非常に高いオーブン温度が必要
- **アフラトキシン**は、ガスクロマトグラフィー分析の際、十分に揮発しない
- 質量分析ライブラリでは（部分）同定できなかった

TIERED APPROACH:
PROPOSAL TO DEAL WITH UNKNOWN PEAKS

	Proposed tier	Background
Tier 1	Exclusion dependent on sample source	For some samples, it will be possible to exclude the presence of some or all 'TTC excluded classes' on basis of their origin.
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Tier 3	Exclusion by targeted analysis	Analyses designed to detect certain structural elements can be applied.
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Tier 5	Quantification of unknown compounds	For risk assessment, the concentration of the unknown peak in the sample has to be estimated with sufficient accuracy.

階層化アプローチ:
未知のピークに対応するための提案

	階層案	背景
Tier 1	Exclusion dependent on sample source	For some samples, it will be possible to exclude the presence of some or all 'TTC excluded classes' on basis of their origin.
Tier 2	Exclusion by chromatographic technique, sample preparation and/or detection method used or partial identification	Analytical techniques are relatively specific, so that a peak detected can only stem from a certain range of substances. They may also indicate the type of substance without providing a full identification.
階層 3	ターゲット分析により除外	構造上の特定の元素を検出するために設計された分析法が適用され得る
Tier 4	Dietary exposure to food sources containing the unknown peak	Due to nutritional habits, exposure depends heavily on the food type.
Tier 5	Quantification of unknown compounds	For risk assessment, the concentration of the unknown peak in the sample has to be estimated with sufficient accuracy.

EXAMPLES: CUCUMBER

Tier 3 Exclusion by targeted analysis

- Presence organometallics could not be ruled out ?
  - ICP-MS analysis showed normal levels of non-essential elements.

ALL 'EXCLUDED CLASSES' RULED OUT

例： キュウリ

階層 3 ターゲット分析による除外

- 有機金属の存在は排除できない
- 誘導結合プラズマ質量分析により、非必須元素はノーマルレベルであることがわかった

'TTC除外クラス' はすべて無視できる

TIERED APPROACH:
PROPOSAL TO DEAL WITH UNKNOWN PEAKS

	Proposed tier	Background
Tier 1	Exclusion dependent on sample source	For some samples, it will be possible to exclude the presence of some or all 'TTC excluded classes' on basis of their origin.
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階層化アプローチ:
未知のピークに対応するための提案

	階層案	背景
Tier 1	Exclusion dependent on sample source	For some samples, it will be possible to exclude the presence of some or all 'TTC excluded classes' on basis of their origin.
Tier 2	Exclusion by chromatographic technique, sample preparation and/or detection method used or partial identification	Analytical techniques are relatively specific, so that a peak detected can only stem from a certain range of substances. They may also indicate the type of substance without providing a full identification.
Tier 3	Exclusion by targeted analysis	Analyses designed to detect certain structural elements can be applied.
階層 4	未知のピークを含んでいる食料源への食事暴露	栄養学的な習慣が原因で、暴露量は食品の種類に大きく左右される
Tier 5	Quantification of unknown compounds	For risk assessment, the concentration of the unknown peak in the sample has to be estimated with sufficient accuracy.

EXAMPLES: CUCUMBER

Tier 4 Exposure to food item containing unidentified peak.

- Cucumber intake of 6.5 g/day (UK NDNS 2001) .
- As the unidentified peak could be potentially genotoxic, the TTC value of 0,15 ug/day would apply.
- → no safety concern when 23 µg/kg (23 ppb) cucumber.

例： キュウリ

階層 4　未確認のピークを含む食品への暴露

- 1日6.5 gのキュウリの摂食　(UK NDNS 2001)
- 未知のピークを示す物質が遺伝毒性を持っている可能性があるので、TTC値 0.15ug/日を適用する
- → 23 µg/kg (23 ppb) のキュウリは安全である

TIERED APPROACH:
PROPOSAL TO DEAL WITH UNKNOWN PEAKS

	Proposed tier	Background
Tier 1	Exclusion dependent on sample source	For some samples, it will be possible to exclude the presence of some or all 'TTC excluded classes' on basis of their origin.
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階層化アプローチ:
未知のピークに対応するための提案

	階層案	背景
Tier 1	Exclusion dependent on sample source	For some samples, it will be possible to exclude the presence of some or all 'TTC excluded classes' on basis of their origin.
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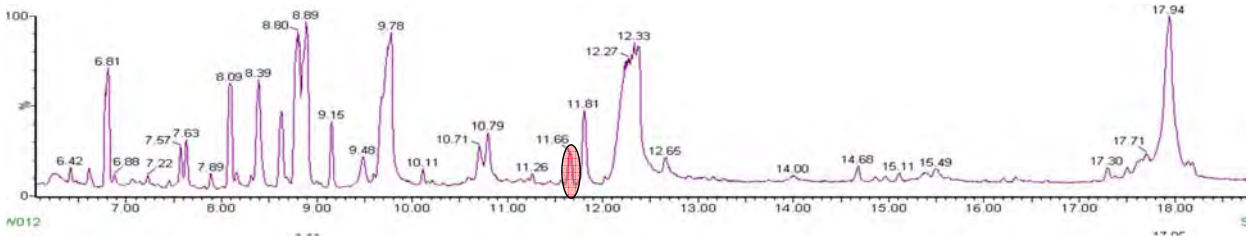
Tier 3	Exclusion by targeted analysis	Analyses designed to detect certain structural elements can be applied.
Tier 4	Dietary exposure to food sources containing the unknown peak	Due to nutritional habits, exposure depends heavily on the food type.
階層 5	未知の化合物の定量化	リスク評価では、試料中に見られる未知のピークの大きさは高精度で評価されなければならない

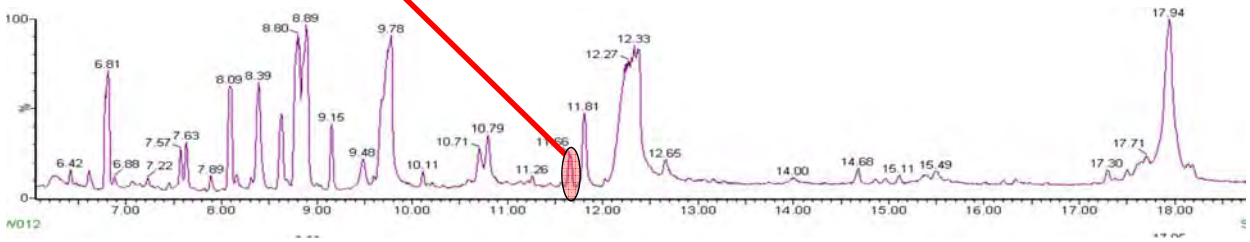
EXAMPLES: CUCUMBER



pesticide screen of cucumber extracts by GC-MS

例： キュウリ

新たなピークが検出された



ガスクロマトグラフ質量分析によるキュウリ抽出物の農薬スクリーン

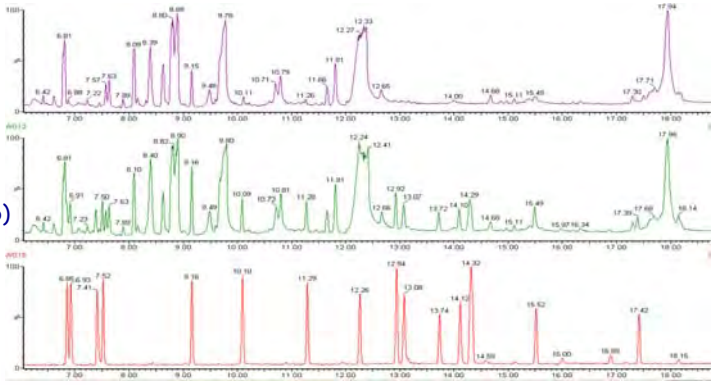
EXAMPLES: CUCUMBER

Tier 5 Quantification

Unspiked cucumber

Cucumber spiked with standards at 23 µg/kg (23 ppb)

Standard solution in solvent



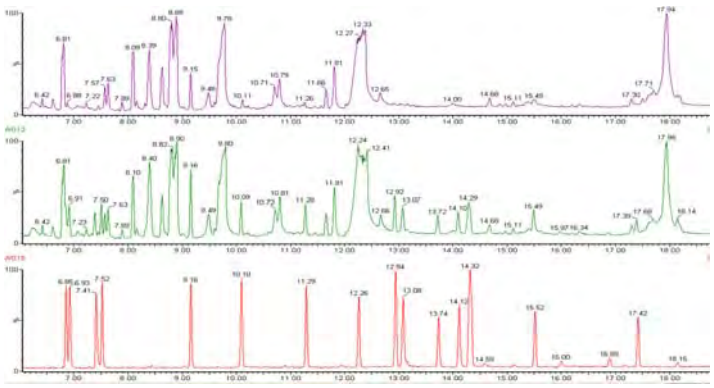
例： キュウリ

階層 5　定量化

未混入のキュウリ抽出物

23 µg/kg (23 ppb)の標準液を混入されたキュウリ抽出物

溶媒中の標準物質（溶体）



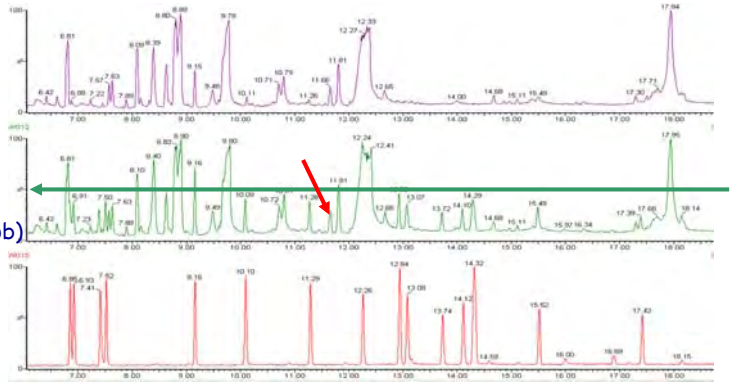
EXAMPLES: CUCUMBER

Tier 5 Quantification

Unspiked cucumber

Cucumber spiked with standards at 23 µg/kg (23 ppb)

Standard solution in solvent



Mean response (peak height) of spiked substances is set as the level of concern at 23 µg/kg (23 ppb)

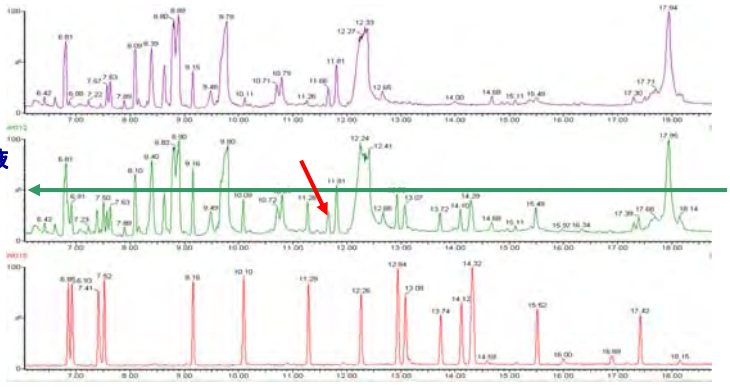
例： キュウリ

階層 5　定量化

未混入のキュウリ抽出物

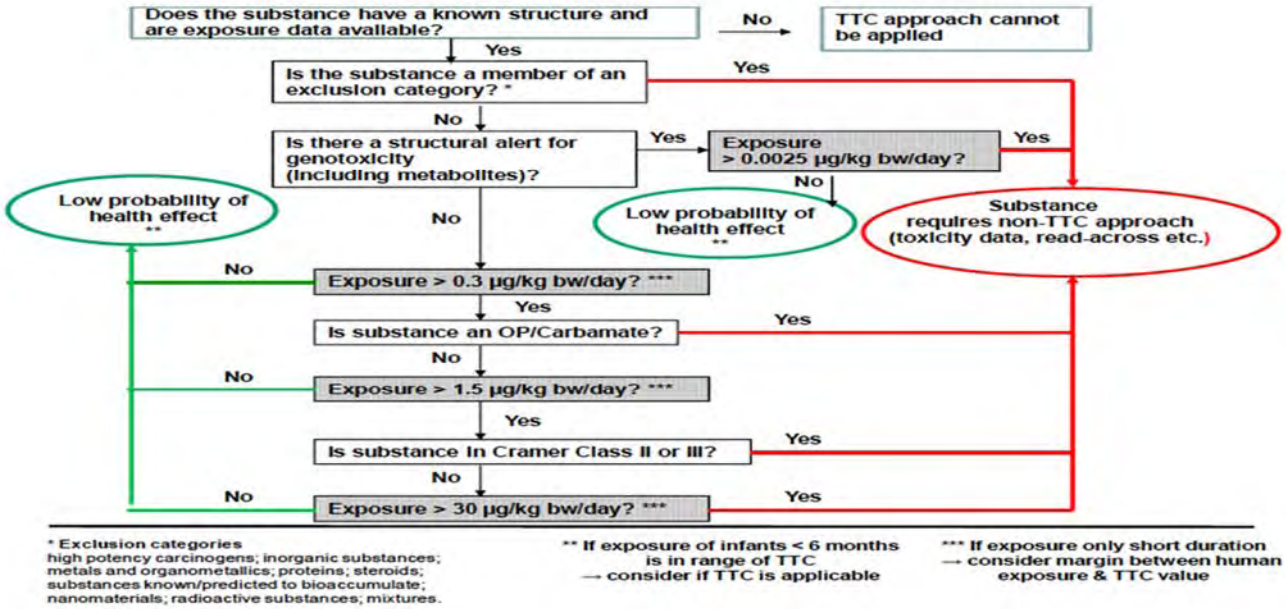
23 µg/kg (23 ppb)の標準液を混入されたキュウリ抽出物

溶媒中の標準物質（溶体）



混入された物質の平均応答（ピークの高さ）は23 µg/kg (23 ppb)の懸念レベルとして設定された

Generic scheme for the application of the TTC approach

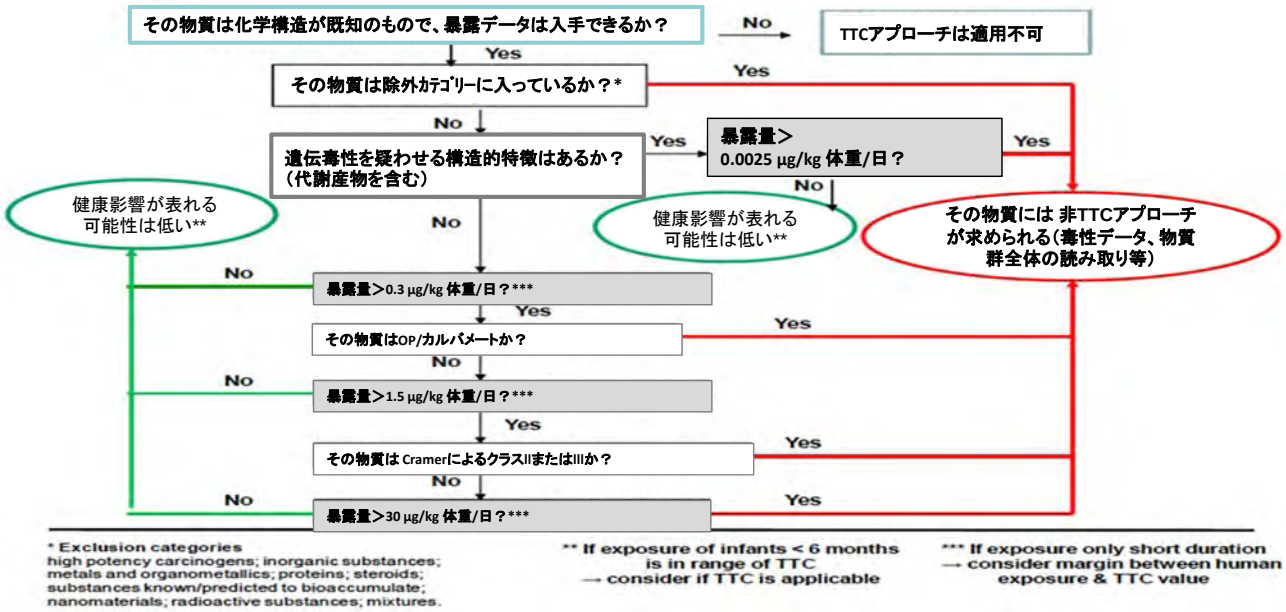


* Exclusion categories
high potency carcinogens; inorganic substances; metals and organometallics; proteins; steroids; substances known/predicted to bioaccumulate; nanomaterials; radioactive substances; mixtures.

** If exposure of infants < 6 months is in range of TTC → consider if TTC is applicable

*** If exposure only short duration → consider margin between human exposure & TTC value

TTCアプローチの適用のための一般的なしくみ



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