Application of TTC concept in the safety evaluation of Food Contact Materials (FCM)

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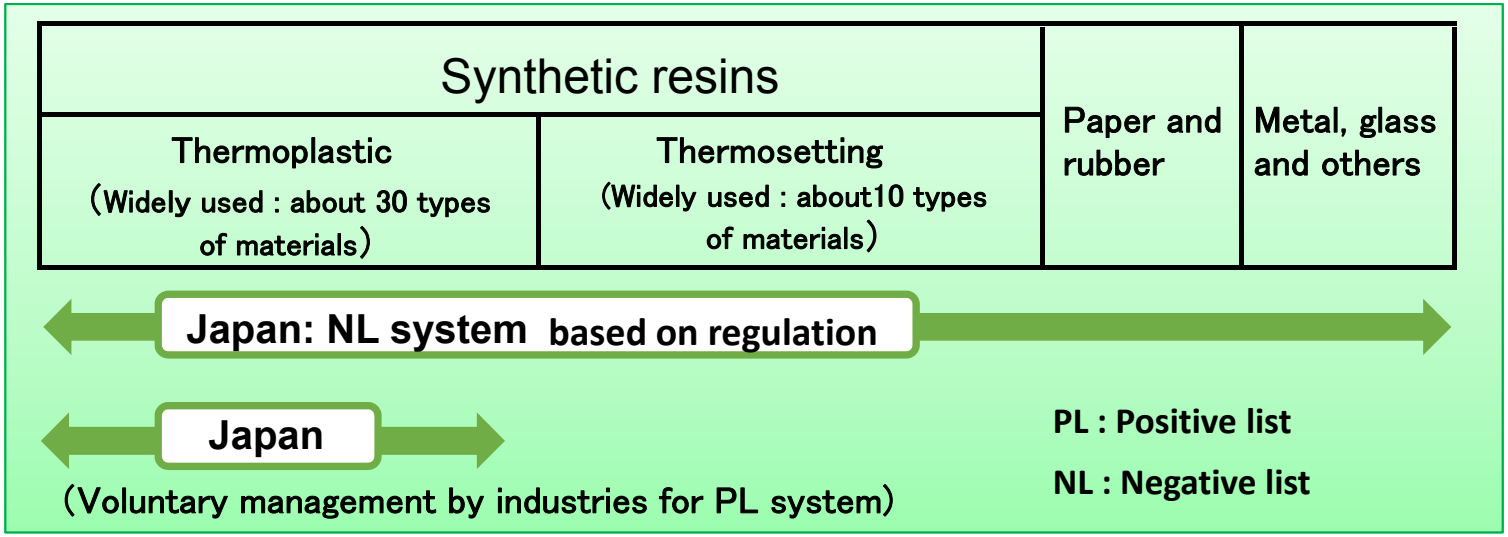
Regulation of Food Contact Materials (FCM*) in Japan

*FCM is defined as Food Utensils, Containers and Packaging (UCP) in the Act

The term “utensils” and ”containers and packaging“ defined in Article 4 of Food Sanitation Act

④ The term “**utensils**" as used in this Act shall mean tableware, kitchen utensils, and other machines, implements, and other articles which are used for collecting, producing, processing, cooking, storing, transporting, displaying, delivering, or consuming food or additives and which come into direct contact with food or additives.

⑤ The term "**containers and packaging**" as used in this Act shall mean articles which contain or wrap food or additives and are offered "as is" when delivering food or additives.



Current situation

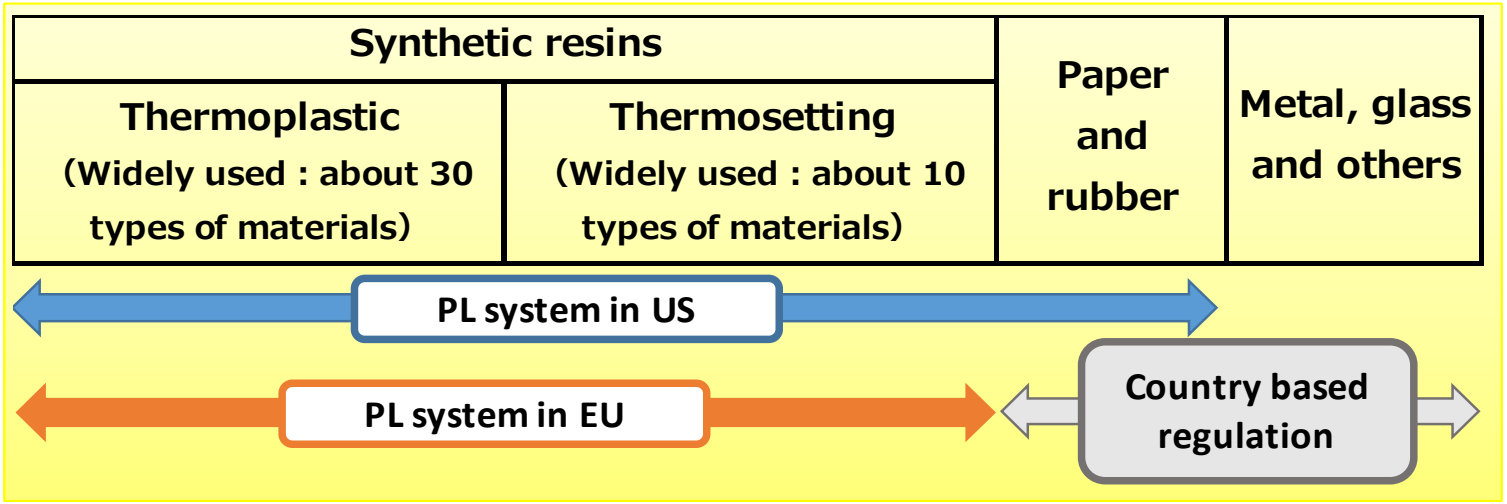
- Regulation based on **NL system** – Only limited substances are restricted for use
- **Voluntary management** by the industries

Secure Safety

Revision for Regulation of FCM
(Introduction of PL system)

Issues

- In EU and US, the regulation is **based on positive list (PL) system**, which prohibits the use of substances other than those approved for use based on the risk assessment (RA) .
- The substances whose use is not permitted in foreign countries such as EU and US **cannot be regulated immediately unless individual specifications and standards are set.**
- New institutional design is required considering the current situation including diversification of products, increase of imported products, and international harmonization.



Introduction of PL system

Revision of Food Sanitation Act : Promulgated on June 13th, 2018 →
Enter into force within two years from promulgation date
Scope : **Synthetic resins**

Revision for Regulation of FCM
(Introduction of PL system)

Risk Assessment in Japan's PL system

Scope : **Synthetic resins**

Risk assessment

While risk assessment (RA) is conducted by the Food Safety Commission of Japan (FSCJ), consistency with global trends should be considered for the assessment method and data required for assessment. RA is an extremely important element including a substance in the PL. A rational and scientific RA method that is consistent with global trends should be established urgently. As the number of candidates for prospective inclusion in the list is expected to be substantial, that process would enable the RA of such substances within a certain period of tine (Report by the Committee on the Regulation of Food Utensils, Containers and Packaging, June 16, 2017 MHLW)

Following the introduction of PL system,
risk management agencies will request for RA on a continuous basis

Develop RA guideline

- ✓ International harmonization → Review **EU and US risk assessment guidelines** where the positive list systems are already introduced
- ✓ To ensure **fair and transparent** RA → **Identify** data necessary for RA

Safety Assessment (SA) for FCM (1)

(Datasets requested based on levels of migrant in food)

- FCM contain various substances (raw materials, impurities contained in raw materials and substances unintentionally produced during manufacturing processes), and these substances from FCM may migrate into food
- However, the amount of substances migrating from FCM is generally low
  - ✓ Initially, the substances were not intended to migrate to food.
  - ✓ The substances were not intended to have technical effects in food.

- In EU and US, toxicity tests required for SA are determined based on the amount of substances migrating to foods (exposure levels) derived from migration tests
- Industries also support the above approach

⇒ **To estimate the exposure (the levels of migrant in diet) of target substance, identify the amount of migrants from the migration tests using food simulants**

⇒ **The toxicity data should be requested based on exposure category which is classified by levels of migrant in diet**

Safety Assessment (SA) for FCM (2)

(Datasets requested based on levels of migrant in food)

How to set up a threshold value for each exposure category ?

Summary table of toxicity tests required for the SA of FCM
based on exposure category (classified by levels of migrant in diet)

Levels of migrant in diet (mg/kg food)	0.0005 (0.5ppb)	0.05 (50ppb)	1 (1ppm)	5 (5ppm)
EU (EFSA)	Genotoxicity	Genotoxicity Subacute toxicity		Genotoxicity Subacute toxicity Reproductive toxicity Developmental toxicity Chronic toxicity Carcinogenicity Pharmacokinetics
US (FDA)	– (Information search with focus on any reports concerning potential carcinogenicity)	Genotoxicity	Genotoxicity Subacute toxicity	Genotoxicity Subacute toxicity Reproductive toxicity Developmental toxicity Chronic toxicity Carcinogenicity Pharmacokinetics

Use of the concept of Threshold of Toxicological Concern (TTC) !

Threshold of Toxicological Concern : TTC

- TTC is an approach to obtain the exposure levels of no concern to human health concerning trace substances contained in food. It is based on a concept that the probability of adverse effects to human health caused by a substance is extremely low below a certain level of exposure.
- Using the toxicity data for chemicals with structural similarities, the levels of exposure that would not possibly cause human health effect (TTC) is established.
- TTC has been used for chemical substances of which intakes or exposure levels are very low, and for which it is difficult to obtain toxicological data from animal studies.
- Application of TTC concept
  - ✓ Threshold of Regulation (TOR) for substances present in food contact materials (FDA)
  - ✓ Safety assessment of flavoring agents（JECFA）
  - ✓ 'Uniform Limit' on positive list system for pesticides and others
  - ✓ Impurities for pharmaceutical chemicals （ICH-M7）

Establishment of exposure category and required toxicity tests (draft)

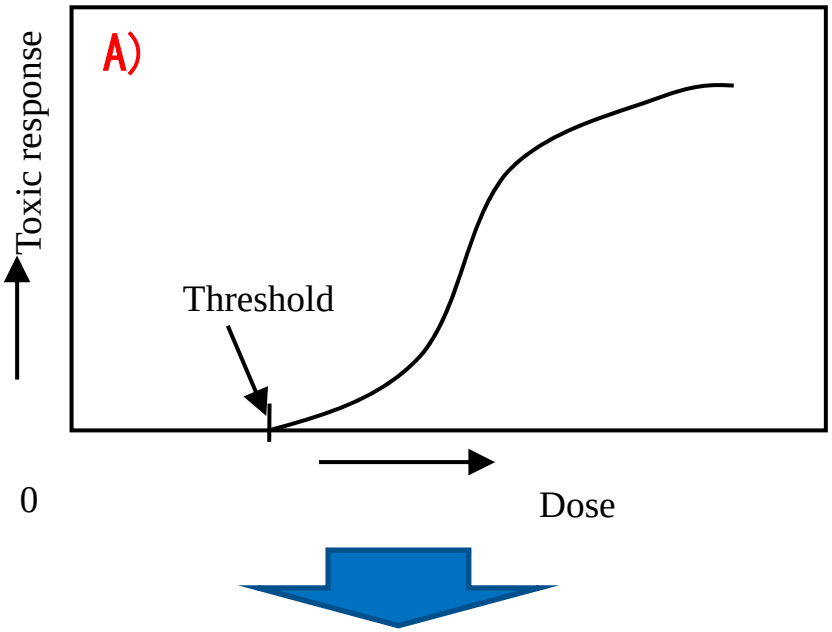
- Exposure category (classified by levels of migrant in diet) and toxicity tests required for assessment constructed by considering the situation in EU and US.

Category based on migration levels in diet		Toxicity study
Category I	Toxicity data is not required	— ※
Category II	General toxicity data is not required	Genotoxicity
Category III	General toxicity data (at screening level) is required	Genotoxicity Subacute toxicity
Category IV	Full toxicity data is required	Genotoxicity Subacute toxicity Reproductive toxicity Developmental toxicity Carcinogenicity Pharmacokinetics

※Submit information on genotoxicity and carcinogenicity based on available data

SA on threshold and non-threshold toxicity

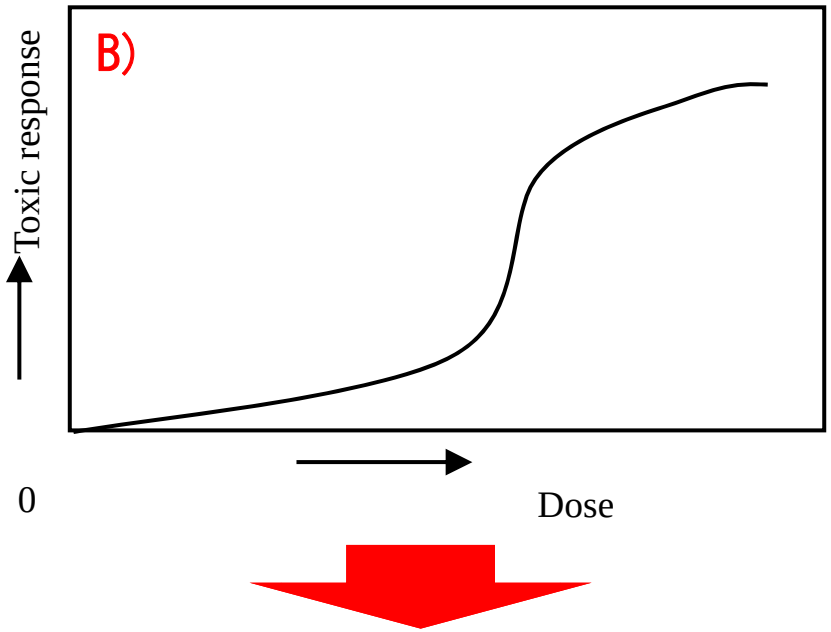
A） Toxicity with threshold
（non-genotoxic carcinogen）



No safety concern if the exposure is below the threshold

Acceptable daily Intake (ADI) and
Tolerable daily intake (TDI) are derived

B） Non-threshold toxicity
（**genotoxic carcinogen**）



Safe threshold cannot be established

Virtually safe dose (VSD) is derived

※ Risk is likely to be negligible if the exposure is below the VSD

Establishment of exposure category and required toxicity tests (draft)

- Exposure category (classified by levels of migrant in diet) and toxicity tests required for assessment constructed by considering the situation in EU and US.

Category based on migration levels in diet		Toxicity study
Category I	Toxicity data is not required	— ※
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Threshold Value for Category I／Category II

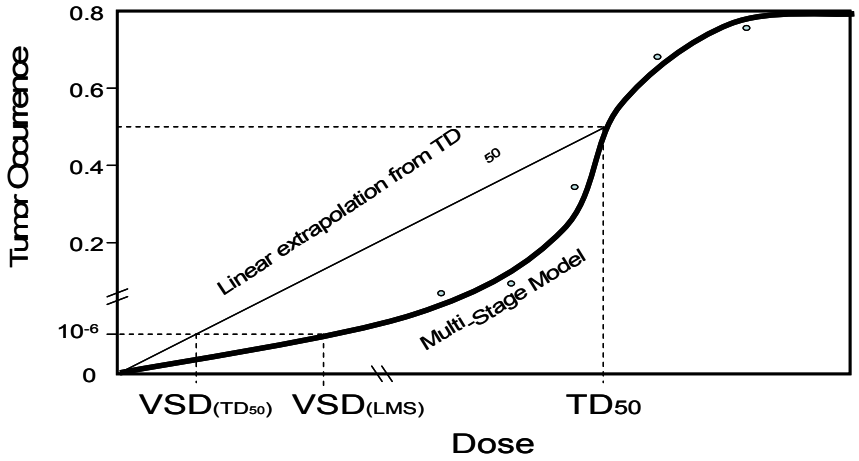
Establish the dietary concentration **at 0.5 μg/kg** based on Virtually safety dose (VSD) extrapolated from carcinogenic potency TD_{50}（dose that caused cancer in 50% of the animals）

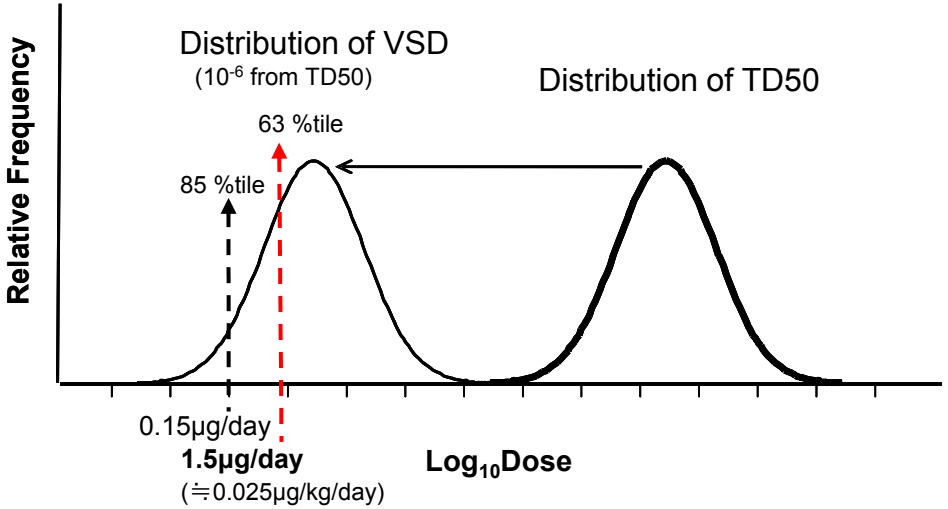
＜Rationale for setting＞

- Threshold of Regulation（TOR） （US FDA, 1993 and 1995）
  - TOR criteria was derived not to exceed 0.5 ppb (μg/kg) food contact material in the diet
  - Under the TOR, food contact substances (FCS) is subject to exemption when the levels of FCS in food is below the TOR
  - Food Contact Notification also adopts TOR. When FCS does not exceed 0.5 ppb in the diet, existing information on the substance is required (no evidence that the substance is carcinogenic or no structural basis for suspecting that the substance is carcinogenic). (=Toxicity test is not required)
- Uniform limit for agricultural chemical residue（MHLW）
  - Established uniform limit of 0.01 ppm (mg/kg) based on TOR
  - Applied to agricultural chemicals for which the standards are not set

TOR = 1.5μg/person/day

VSD (cancer risk of 1 in a million) calculated by linear extrapolation from TD50. Distribution of TD50 was obtained from 477 chemicals in Carcinogenic Potency Database (CPDB)





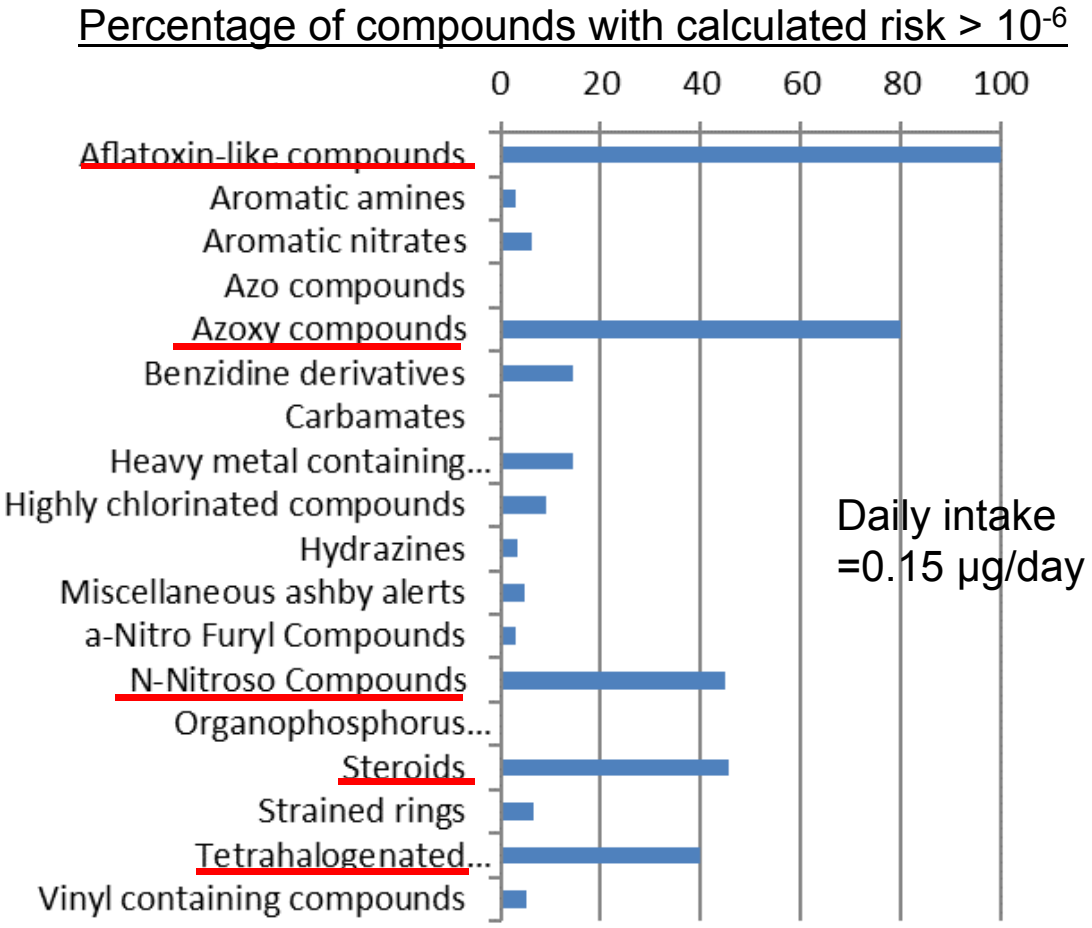
Percentage of presumed carcinogenic compounds and compounds with calculated risk < 10^{-6}(10^{-5})

(Modified from Munro(1990))

Threshold value	100%	50%	20%	10%	100%	50%	20%	10%
μg/day	10-6 risk				10-5 risk			
0.15	86	93	97	99	96	98	99	99
0.3	80	90	96	98	94	97	99	99
0.6	74	87	95	97	91	96	98	99
1.5	63	82	93	**96**	86	96	97	**99**
3	55	77	91	95	80	90	96	98
6	46	73	89	95	74	87	95	97

1.5μg/person/day ≒0.025μg/kg・bw/day ≒0.5 ppb

TTC values for compounds with chemical structure of concern due to their high gentoxicity



TTC value of **1.5μg/day is not sufficient for** substances with structural alerts for genotoxicity

Constructed based on Table1 of R. Kroes et al. Food. Chem. Toxicol 42, 65-83(2004)

⇒ For category I, available information on genotoxicity is required
(＝Toxicity study is not required. Toxicity test results can be used)

Establishment of exposure category and required toxicity tests (draft)

- Exposure category (classified by levels of migrant in diet) and toxicity tests required for assessment constructed by considering the situation in EU and US.

Migration levels in diet
0.5 μg/kg

Category based on migration levels in diet		Toxicity study
Category I	Toxicity data is not required	— ※
Category II	General toxicity data is not required	Genotoxicity
Category III	General toxicity data (at screening level) is required	Genotoxicity Subacute toxicity
Category IV	Full toxicity data is required	Genotoxicity Subacute toxicity Reproductive toxicity Developmental toxicity Carcinogenicity Pharmacokinetics

※Submit information of genotoxicity and carcinogenicity based on available data

Threshold Value for Category II／Category III（1）

The dietary concentration was derived at 0.05 mg/kg based on Cramer structural class III value of human exposure, threshold 0.09 mg/person/day

＜ Rationale for setting＞

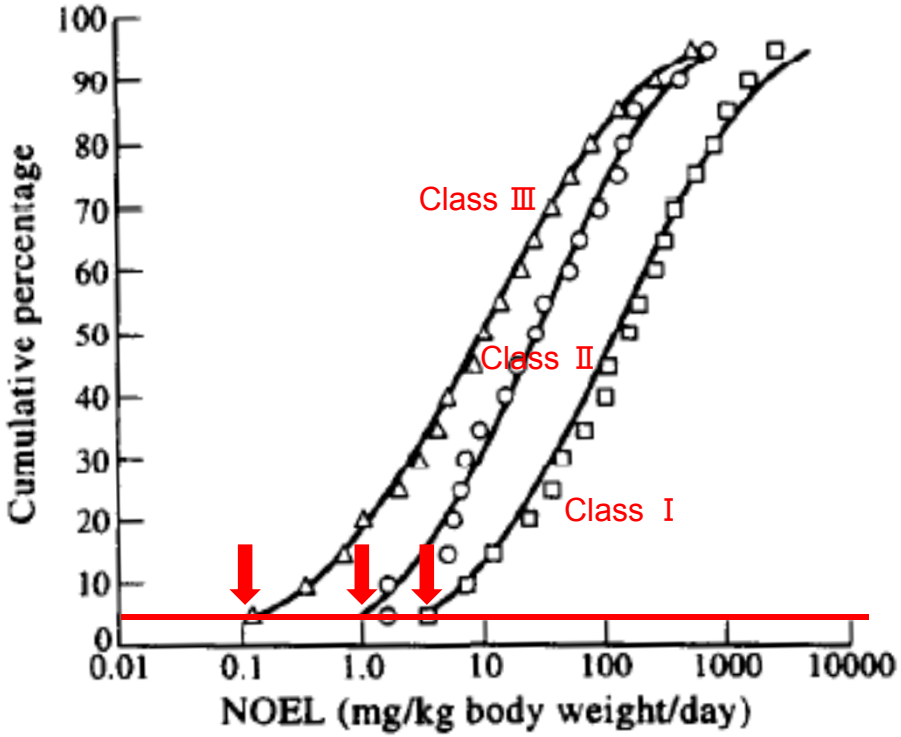
- TTC levels for Cramer class III substances
  - Non-carcinogenic effect of chemical substances were analyzed using dataset of 613 chemicals （Munro(1996)）
  - TTC of 0.09 mg/person/day was established based on analysis of 448 substances of Cramer class III
  - The TTC value is reasonably conservative compared with that of the class III substances reported in other documents
- The corresponding dietary concentration
  - The dietary concentration, assuming that daily intake per person is 2 kg

0.09 mg/person/day ÷ 2 kg = 0.045 mg/kg ≒ 0.05 mg/kg

Threshold Value for Category II／Category III（2）

＜Establishment of TTC value（Munro (1996)）＞

- Database of 613 substances including industrial chemicals, pharmaceuticals, food ingredients
- Classification based on chemical structure（Cramer classification)
- NOEL for non-carcinogenic endpoint (derived from subacute, chronic, reproductive and developmental toxicity)



（Munro (1996)）

For each Cramer class chemicals, 5th percentile of the cumulative distribution of NOAELs

Incorporate safety factor and assume body weight

TTC value of class Ⅰ/Ⅱ/Ⅲ

Threshold Value for Category II／Category III（3）

- Munro(1996) and TTC exposure limits

Cramer class	Number of chemicals	5%ile NOEL (mg/kg bw/day)	TTC value※ (mg/person/day)
Ⅰ	137	3.0	1.8
Ⅱ	28	0.91	0.54
Ⅲ	448	0.15	0.09

Use as a basis for setting the threshold value between Category Ⅱ/Ⅲ

※TTC was derived from 5%ile of NOEL, safety factor of 100, and 60 kg human body weight

＜Cramer Class（Consists of a “decision tree” of 33 questions Cramer et al.,1978）＞

Class Ⅰ： Substances with simple chemical structure, for which efficient modes of metabolism exist suggesting a low order of oral toxicity

Class Ⅱ： Substances which possess structures that are less innocuous than class I substances, but do not contain structural features suggestive of toxicity like those substances in class III.

Class Ⅲ Substances with chemical structures that permit no strong initial presumption of safety or may even suggest significant toxicity or have reactive functional groups.

Threshold Value for Category II／Category III （4）

＜Points to consider when applying TTC value (Cramer classⅢ) derived by Munro(1996)＞

- The TTC is a threshold value for non-cancer endpoints
  - ⇒ For genotoxic carcinogens, consideration should be taken.
    - → Genotoxicity study is required for Category Ⅱ substances.
- Limitations of the concept of TTC by Munro et. al.
  - ✓ TTC value was derived from the 5th percentile value of the distribution of NOELs.
    - ⇒ Possible toxic effects from exposure to substances that can occur below the TTC value (e.g., neurotoxicity, immunotoxicity, endocrine activity, and bioaccumulation)
  - ✓ Substances not included in dataset examined by Munro et. al.
    - ⇒ TTC approach should not be applied to substances not included in the database (e.g., organometallics, inorganic substances, chemical mixtures, and substances of unknown structure)

Should be taken into consideration on case by case basis.

Substances/Toxic effects to consider when applying TTC (1)
＜ Neurotoxicity＞

- For organophosphate and carbamate compounds, there are reports suggesting that TTC value of 0.09 mg/person/day is not conservative, and the value 0.018 mg/person/day was proposed.（Munro et al., 1999, Kroes et al, 2004, and others）
- Toxicological data was obtained for 18 phosphorous compounds used in utensils, containers and packaging (UCP) made of synthetic resins. None of the ADI/TDI of the substances was below the proposed TTC value.

⇒
- Phosphorous compounds used in UCP made of synthetic resins generally demonstrate low neurotoxicity, and the proposed TTC is considered to be conservative
- On the other hand, for organophosphorous and carbamate compounds, the proposed TTC is not sufficiently conservative

Regardless of exposure category (levels of migrant in diet),

✓ Specific neurotoxicity test is not required

✓ However, when neurotoxicity is suspected on the basis of available information, neurotoxicity test is required additionally.

Substances/Toxic effects to consider when applying TTC (2)

＜ Immunotoxicity ＞

- Toxicological endpoints for the NOELs for the 613 substances in the Munro et al., (1999) was examined. None of the NOELs were based on immunotoxic effects. (EFSA 2012)
- The sensitivity of immunotoxicity was examined by comparison of NOELs and LOELs based on immunotoxic end-points with corresponding NOELs and LOELs based on non-immunotoxic endpoints. （Munro et.al., 1999, Kroes et.al., 2000） It was suggested that immunotoxicity should not be considered a more sensitive endpoint compared to other toxicity endpoints.

⇒ • Immunotoxicity is not a more sensitive endpoints compared to other toxicity

• The TTC value is considered to be conservative for immunotoxicity

Regardless of exposure category (levels of migrant in diet),

✓ Specific immunotoxicity test is not required

✓ However, when immunotoxicity is suspected on the basis of available information, immunotoxicity test is required additionally.

Substances/Toxic effects to consider when applying TTC (3)

< Endocrine mediated activity >

- Uncertainties are identified for low dose effects of endocrine active substance. Currently, there is no agreement among scientist on nonlinear dose-response relationship for low dose effect. (Kroes et.al., 2004 and EFSA 2018)
- It is premature to consider low dose effects of substances with endocrine activity/disrupting properties in the application of TTC approach. TTC approach may possibly applied to the substances other than steroids. (Kroes et.al., 2004 and EFSA 2016)

⇒
- Uncertainties are identified for low dose effects of substance with endocrine activity.
- TTC approach may possibly applied to the substances other than steroids.

Regardless of exposure category (levels of migrant in diet),

✓ Specific endocrine toxicity test is not required

✓ However, when endocrine toxicity is suspected on the basis of available information, endocrine toxicity test is required additionally.

Substances/Toxic effects to consider when applying TTC (4)

＜ Bioaccumulation（1）＞

- Specific considerations on metabolism/bioaccumulation are not necessary excluding potent substances that show large species differences in bioaccumulation such as polyhalogenated-dibenzo-p-dioxins. (Kroes et al., 2004)
- Out of 448 substances classified in Cramer class Ⅲ, thresholds for high/low bioaccumulative substances were derived separately. It was concluded that there is no need to exclude bioaccumulating substances from the TTC concept (Leeman et al., 2016)

⇒ **Category Ⅰ/Ⅱ** : TTC value for Cramer class III is derived with datasets in which highly bioaccumulative substances are present. Therefore, TTC approach is considered to be applicable excluding substances that require special consideration

✓ Test data evidence for bioaccumulative potential such as ADME tests are not necessary

(However, for substances with high bioaccumulative potential such as polyhalogenated dibenzo-p-dioxin, substances with high log Pow value※, or substances that require special consideration (e.g., chemical structure), test is required.)

※ Octanol/water partition (log Po/w) coefficient

Substances/Toxic effects to consider when applying TTC (5)

＜ Bioaccumulation（2）＞

⇒ **Category Ⅲ** : The exposure exceeds the TTC value (Crammer class III), and therefore, consideration should be taken on bioaccumulation

- ✓ log Pow ＜3 : Generally, test is not required
  (However, for substances that require special consideration (e.g., chemical structure). Test data evidence for accumulative potential such as kinetic studies（e.g., ADME tests）may be required
- ✓ log Pow ≧3 : Test data evidence for accumulative potential（e.g., ADME tests）are required

⇒ **Category Ⅳ** : Pharmacokinetics study is included in the test data package

- ✓ Assessment based on the results of pharmacokinetics study

Substances/Toxic effects to consider when applying TTC (6)

＜ Metals, Inorganic substances, Chemical mixtures and others＞

- TTC approach is not applicable for substances not included in the database of Munro et al. (1996) due to limitations of datasets. （Kroes et al, 2004, EFSA 2012 and others）
- However, for chemical mixtures, TTC approach can be applied only in cases where the mixtures do not include substances unsuitable for TTC approach. (EFSA 2012 and others)

⇒
- TTC approach should not be applied to substances not included in the database of Munro et al.
- In some cases, TTC approach can be applied to chemical mixtures when they do not include substances unsuitable for TTC approach.

✓ Metals, Inorganic substances and protein :
Category Ⅰ/Ⅱ/Ⅲ → Toxicity test for Category III substance is required

✓ Mixtures of chemical substances :
The same procedures as metals, inorganic substances and protein.
(However, toxicity test is required according to exposure category when the following cases are identified: toxic effects that need consideration /substances unsuitable for TTC approach are not included)

✓ Emerging technology materials （nanomaterials and others) : case by case approaches are required

Establishment of food category and required toxicity tests (draft)

- Exposure category (classified by levels of migrant in diet) and toxicity tests required for assessment constructed by considering the situation in EU and US.

Migration levels in diet

0.5 μg/kg

0.05 mg/kg

Category based on migration levels in diet		Toxicity study
Category I	Toxicity data is not required	— ※
Category II	General toxicity data is not required	Genotoxicity
Category III	General toxicity data (at screening level) is required	Genotoxicity Subacute toxicity
Category IV	Full toxicity data is required	Genotoxicity Subacute toxicity Reproductive toxicity Developmental toxicity Carcinogenicity Pharmacokinetics

log Pow

※Submit information on genotoxicity and carcinogenicity based on available data

Threshold value for Category Ⅲ ／Ⅳ

Migration levels in diet was established at 1 mg/kg

＜Studies used for the establishment of the level＞

Toxicological endpoint	Converted to concentration in diet	Study	Reference
Reproductive and developmental toxicity	**15** mg/kg	Barlow (1994)	Toxicity test data required in EU
Chronic toxicity	220 substances ≧**1** mg/kg, excluding 5 pesticides	Frawley (1967)	Toxicity test data required in US
Developmental toxicitiy	Industrial chemicals **3** mg/kg *（Rat 537 substances） **2.9** mg/kg *（Rabbit 150 substances）	van Ravenzwaay (2017)	
Reproductive and developmental toxicity	15 substances **1.2** mg/kg *	EFSA (2012)	

- International harmonization

  - Toxicity data including reproductive and developmental toxicity, and carcinogenicity is required（US： ≧ 1 mg/kg food, EU： ≧ 5 mg/kg food）

* Converted by FSCJ based on literatures

Establishment of food category and toxicity tests（draft)

- Exposure category (classified by levels of migrant in diet) and toxicity tests required for assessment constructed by considering the situation in EU and US.

Migration levels in diet	Category based on migration levels in diet		Toxicity study
0.5 μg/kg	Category I	Toxicity data is not required	— ※
	Category II	General toxicity data is not required	Genotoxicity
0.05 mg/kg	Category III	General toxicity data（at screening level） is required	Genotoxicity Subacute toxicity
1 mg/kg	Category IV	Full toxicity data is required	Genotoxicity Subacute toxicity Reproductive toxicity Developmental toxicity Carcinogenicity Pharmacokinetics

log Pow

※Submit information on genotoxicity and carcinogenicity based on available data

Levels of Migrant in Diet and Required Tests

Comparison among EU, US and Japan(draft)

Levels of migrant in diet (mg/kg food)	0.0005 (0.5ppb)	0.05 (50ppb)	1 (1ppm)	5 (5ppm)
EU (EFSA)	Genotoxicity	Genotoxicity Subacute toxicity		Genotoxicity Subacute toxicity Reproductive toxicity Developmental toxicity Carcinogenicity Pharmacokinetics
US (FDA)	– (Information search with focus on any reports concerning potential carcinogenicity)	Genotoxicity	Genotoxicity Subacute toxicity	Genotoxicity Subacute toxicity Reproductive toxicity Developmental toxicity Carcinogenicity Pharmacokinetics
Japan	– (Information search with focus on any reports concerning potential carcinogenicity)	Genotoxicity	Genotoxicity Subacute toxicity	Genotoxicity Subacute toxicity Reproductive toxicity Developmental toxicity Carcinogenicity Pharmacokinetics

※Submit information on genotoxicity and carcinogenicity based on available data

Thank you very much
for your attention !