

**Evaluation of Flavoring Substances
by the Joint FAO/WHO Expert
Committee on Food Additives
(JECFA)**

**Tokyo, Japan
November 9, 2007**

Ian C. Munro Ph.D., F.A.T.S., FRCPath.

**フレーバー物質に関するJECFA(the
Joint FAO/WHO Expert
Committee on Food Additives)
評価とアップデート**

**Tokyo, Japan
November 7, 2007**

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JECFA PRINCIPLES FOR SAFETY EVALUATION OF FLAVORS

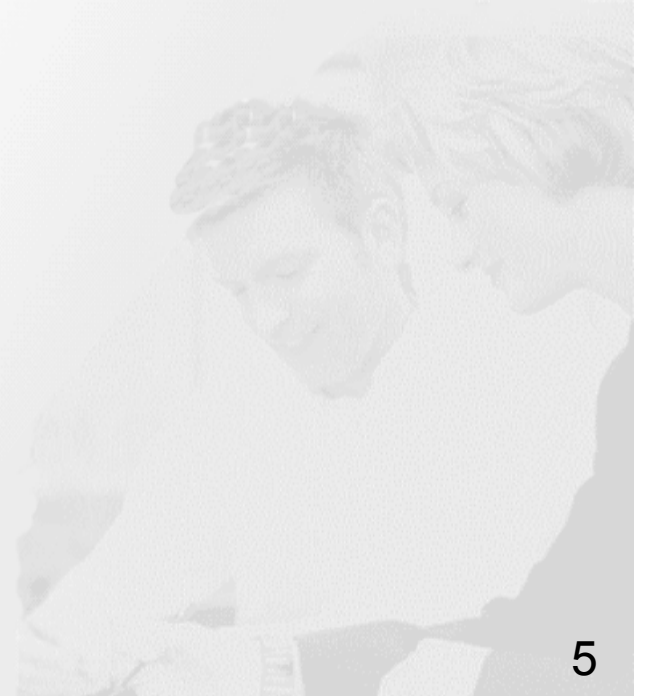
- 1972 - Safety evaluation of flavoring substances warrants special consideration because of use patterns and low human intake**
- 1987 - Knowledge of structure-activity relationships and metabolism plays a key role along with intake data in the safety evaluation**
- 1996 - JECFA adopted a new procedure for the safety evaluation of flavoring substances**

フレーバー物質の安全性評価のJECFA原則

- 1972年 フレーバー物質の安全性評価には、その使用パターンおよびヒトの摂取量が低いことから特別な考慮をすることが可能である
- 1987年 構造活性相関および代謝の知見は、安全性評価の中では、摂取量データとともに主要な役割を果たすものである
- 1996年 JECFA はフレーバー物質の安全性評価について、新しい手順を採択。

KEY ELEMENTS OF THE JECFA SAFETY EVALUATION PROCEDURE

- INTAKE
- METABOLISM (SAR)
- TOXICITY DATA



安全性評価手順の重要な要素

- 摂取量
- 代謝(構造活性相関)
- 毒性データ

USE OF TOXICITY DATA

- **Humans are exposed at low levels to a large number of substances in the food supply**
- **The requirement for toxicological data needs to be considered in the light of knowledge of exposure, metabolism, chemical structure and existing toxicological data**
- **Toxicity data are not available on all flavoring substances; however, data exist on one or more members of a group of structurally related substances**

毒性データの利用

- 人は食事を通じ低レベルで数多くの物質に暴露される
- 毒性データが必要かどうかについては、暴露量、代謝、化学的構造、および既存の毒性データに関する知見に照らして検討する必要がある
- 全てのフレーバー物質について毒性データが入手できるわけではない；
しかし、通常は構造的に近似した物質グループの中の1つあるいはそれ以上の物質に毒性データが存在する

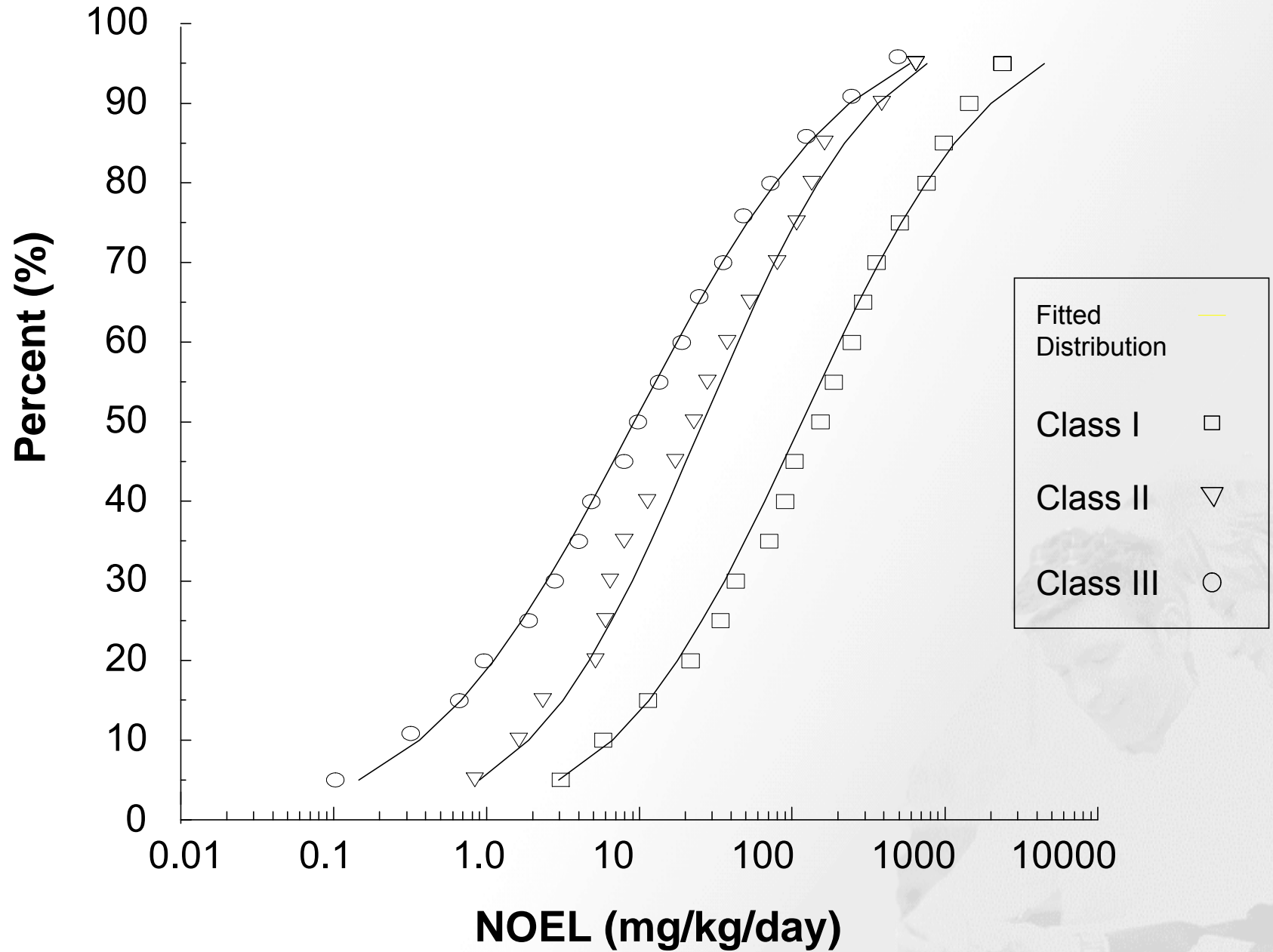
CONCEPT OF THRESHOLDS

The JECFA safety evaluation procedure incorporates the concept of human toxicity thresholds, which are used to evaluate potential for toxicity of flavoring substances

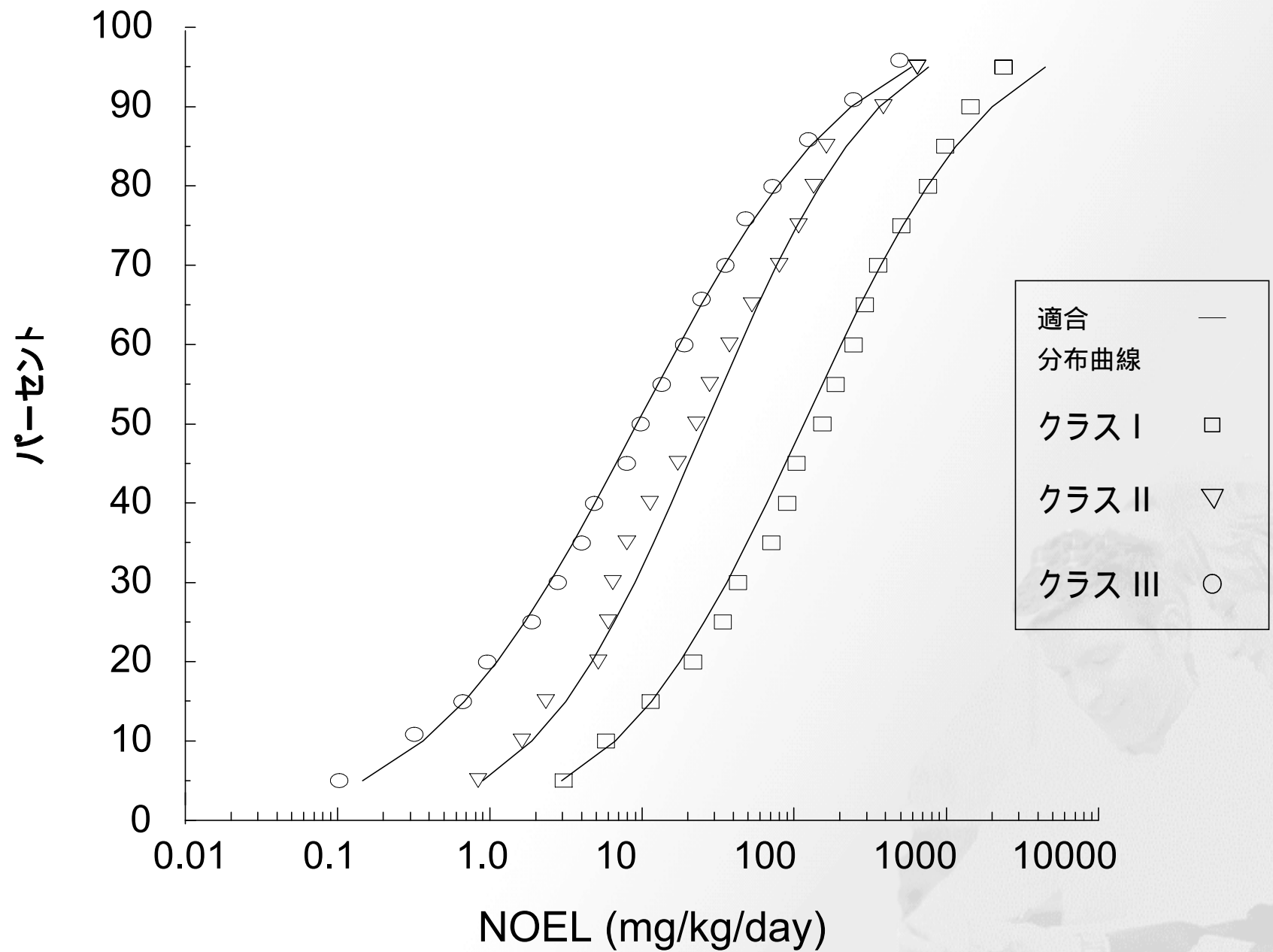
閾値の概念

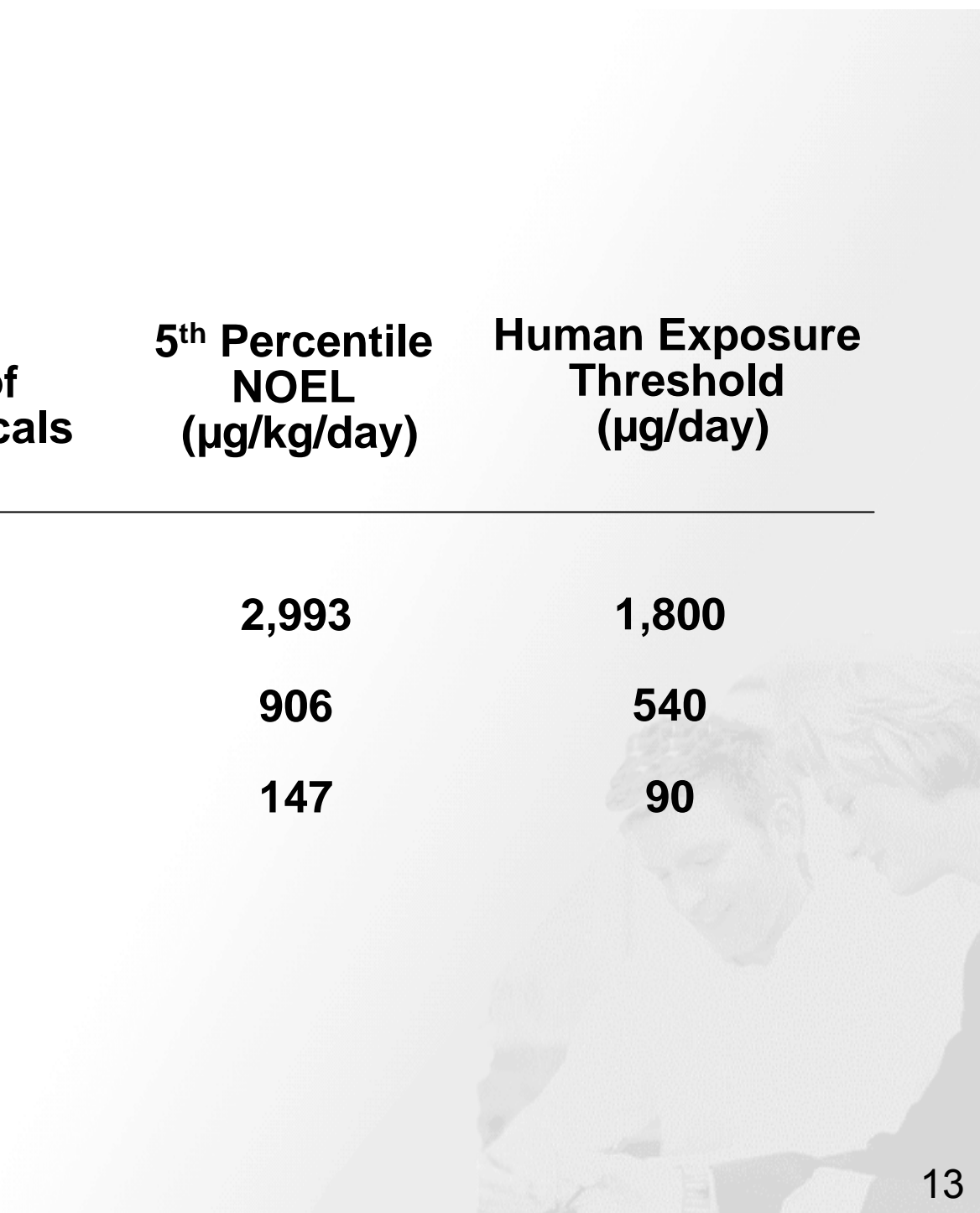
JECFA の安全性評価手順は ヒトへの毒性閾値の概念をくみこんでおり、この概念はフレーバー物質が毒性を示す可能性を評価するのに用いられている

CUMULATIVE DISTRIBUTIONS OF NOELs

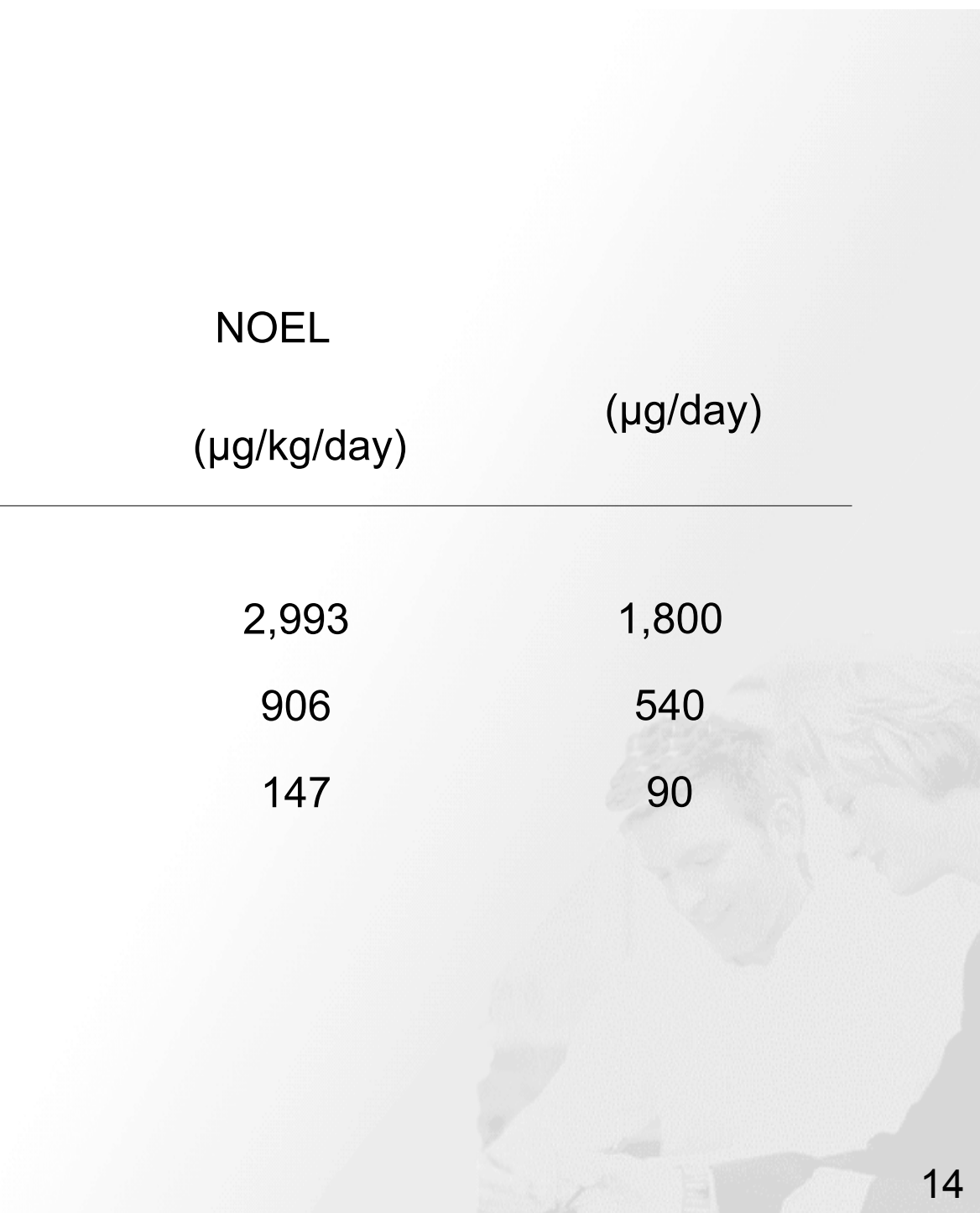


NOELの累積分布

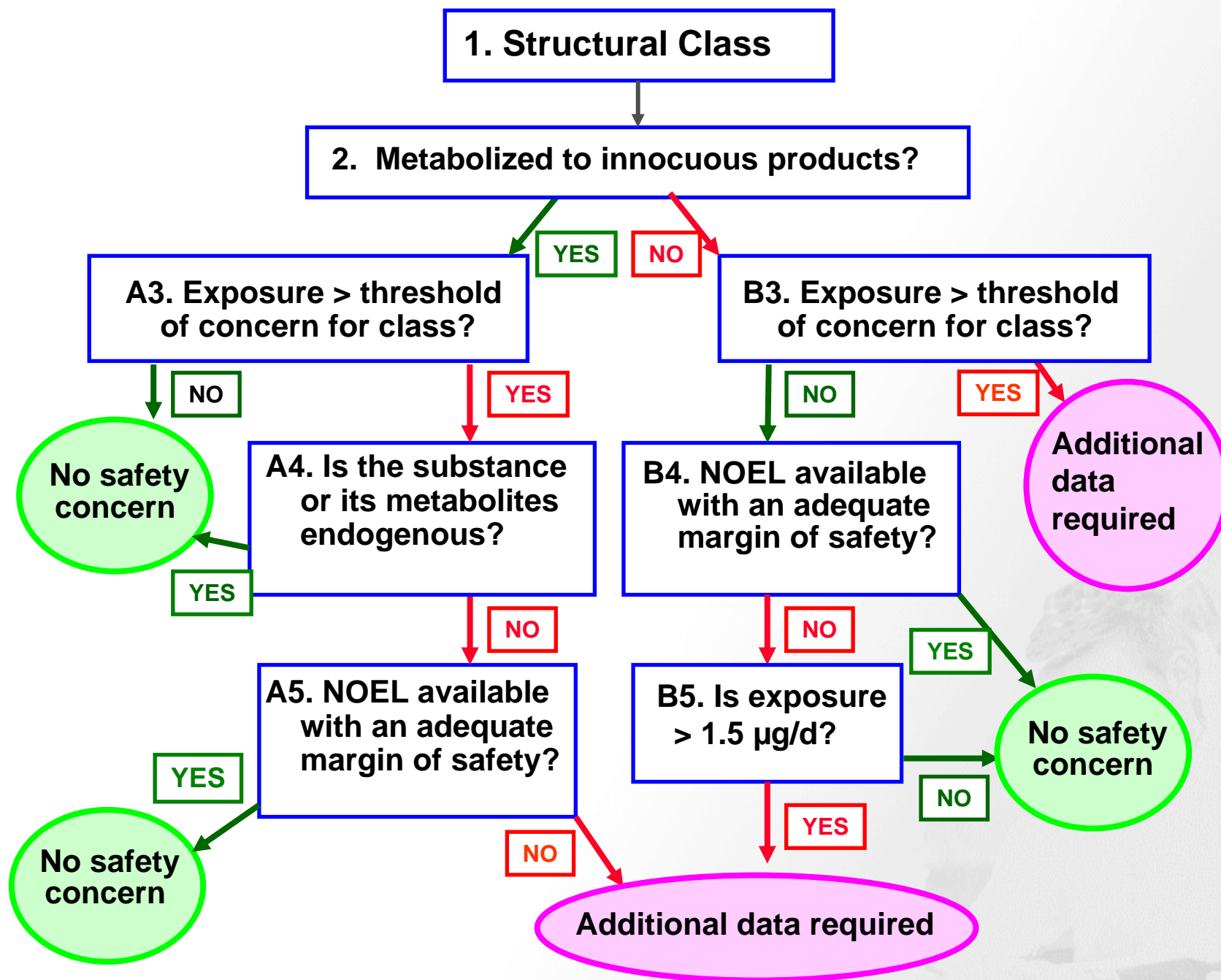


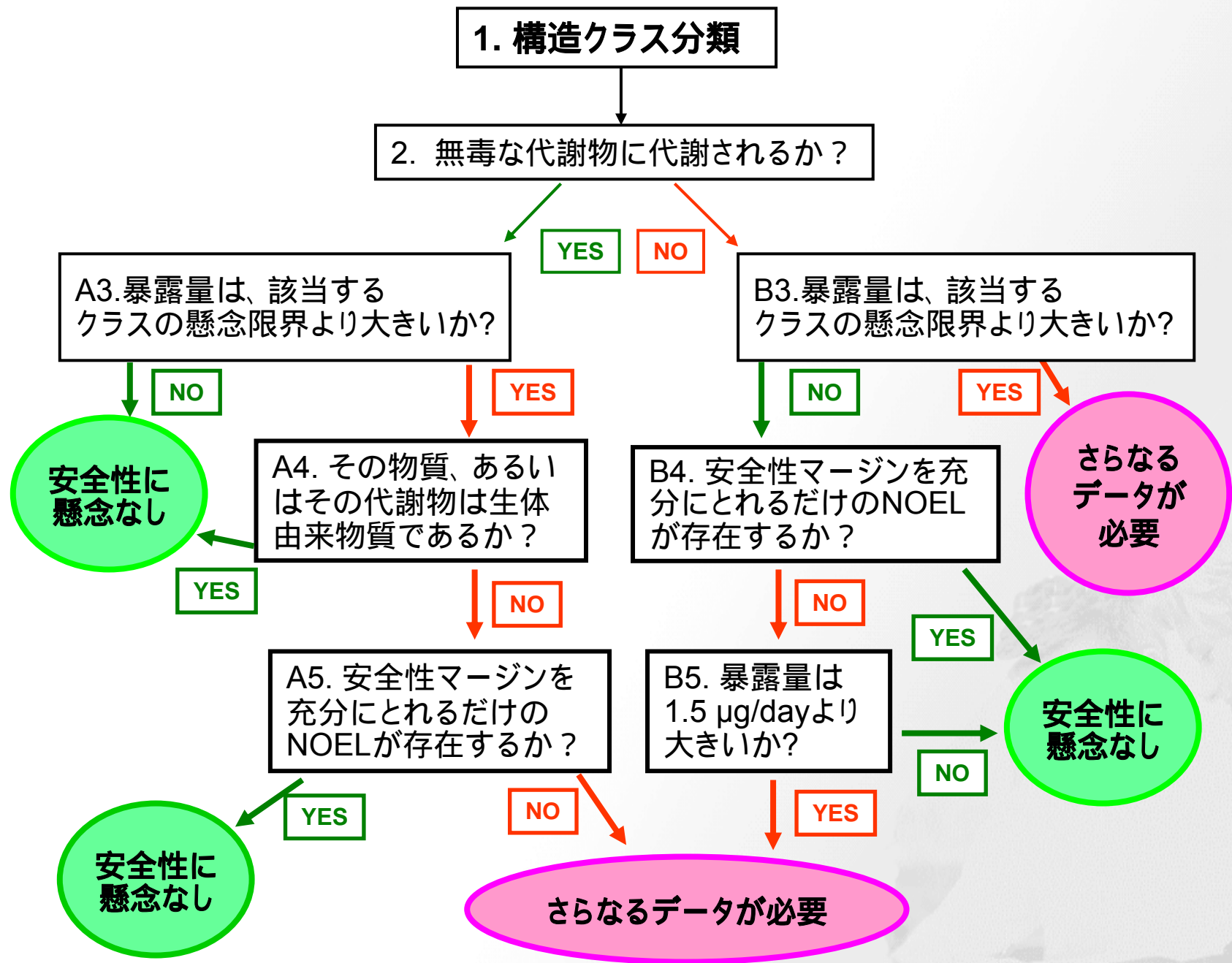


Structural Class	No. of Chemicals	5th Percentile NOEL (µg/kg/day)	Human Exposure Threshold (µg/day)
I	137	2,993	1,800
II	28	906	540
III	447	147	90



構造クラス	化学物質の数	NOEL の 5パーセンタイル値 ($\mu\text{g}/\text{kg}/\text{day}$)	ヒトの暴露閾値 ($\mu\text{g}/\text{day}$)
I	137	2,993	1,800
II	28	906	540
III	447	147	90





FLAVORING SUBSTANCES EVALUATED BY JECFA USING THE PROCEDURE 1996-2007

Flavouring Agents/Group	No. in Group	Structural Class			Year
		I	II	III	
46th Meeting					
Ethyl esters	15	15			1996
Isoamyl alcohol and related esters	11	11			1996
Allyl esters	20		18	2	1996
49th Meeting					
Allyl 2-furoate	1			1	1997
Saturated aliphatic acyclic linear primary alcohols, aldehydes and acids	38	38			1997
Saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and acids	25	22	3		1997
Aliphatic lactones	35	29		6	1997
Esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids	32	32			1997
Esters of aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids	67	66	1		1997
Esters derived from branched-chain terpenoid alcohols and aliphatic acyclic carboxylic acids	26	26			1997
51st Meeting					
Saturated aliphatic acyclic secondary alcohols, ketones, and related saturated and unsaturated esters	39	28	11		1998
Linear and branched-chain aliphatic unsaturated unconjugated alcohols, aldehydes, acids and related esters	42	42			1998
Aliphatic acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances	23	22	1		1998
Carvone and structurally related substances	9	6	3		1998
Ionones and structurally related substances	21	21			1998
Aliphatic acyclic and alicyclic α -diketones and related α -hydroxyketones	22		22		1998
Substances structurally related to menthol	13	8	5		1998

この安全性評価手順を用いてJECFAによって評価された フレーバー物質 (1996年から2007年まで)

フレーバー物質名 / グループ名	グループ内の物質数	構造クラス			開催年
		I	II	III	
46 回会議					
Ethyl esters	15	15			1996
Isoamyl alcohol and related esters	11	11			1996
Allyl esters	20		18	2	1996
49 回会議					
Allyl 2-furoate	1			1	1997
Saturated aliphatic acyclic linear primary alcohols, aldehydes and acids	38	38			1997
Saturated aliphatic acyclic branched-chain primary alcohols, aldehydes and acids	25	22	3		1997
Aliphatic lactones	35	29		6	1997
Esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids	32	32			1997
Esters of aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids	67	66	1		1997
Esters derived from branched-chain terpenoid alcohols and aliphatic acyclic carboxylic acids	26	26			1997
51 回会議					
Saturated aliphatic acyclic secondary alcohols, ketones, and related saturated and unsaturated esters	39	28	11		1998
Linear and branched-chain aliphatic unsaturated unconjugated alcohols, aldehydes, acids and related esters	42	42			1998
Aliphatic acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances	23	22	1		1998
Carvone and structurally related substances	9	6	3		1998
Ionones and structurally related substances	21	21			1998
Aliphatic acyclic and alicyclic α -diketones and related α -hydroxyketones	22		22		1998
Substances structurally related to menthol	13	8	5		1998

FLAVORING SUBSTANCES EVALUATED BY JECFA USING THE PROCEDURE 1996-2007 (CONT'D)

Flavouring Agents/Group	No. in Group	Structural Class			Year
		I	II	III	
53rd Meeting					
Simple aliphatic and aromatic sulfides and thiols	137	97	34	6	1999
Aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups	47	47			1999
55th Meeting					
Cinnamyl alcohol and related flavouring agents	55	50	5		2000
Furfuryl alcohol and related flavouring agents	15		9	6	2000
Phenol and phenol derivatives	48	47		1	2000
Pulegone and related flavouring agents	6	2	4		2000
57th Meeting					
Pyrazine derivatives	41		32	9	2001
Aromatic substituted secondary alcohols, ketones and related esters	38	28	6	4	2001
Benzyl derivatives	37	37			2001
Hydroxy- and alkoxy-substituted benzyl derivatives	46	36	10		2001
Aliphatic acyclic diols, triols and related substances	31	23	5	3	2001
Aliphatic acyclic acetals	10	10			2001
59th Meeting					
Alicyclic primary alcohols, aldehydes acids and related esters	26	26			2002
Phenethyl alcohol, aldehyde, acid and related acetals and esters	43	39		4	2002
Sulfur-containing heterocyclic and heteroaromatic derivatives	30		21	9	2002
Sulfur-substituted furan derivatives	33		18	15	2002
Alicyclic ketones and secondary alcohols	25	6	19		2002
Aliphatic secondary alcohols and ketones	39	11	28		2002

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		I	II	III	
53 回会議					
Simple aliphatic and aromatic sulfides and thiols	137	97	34	6	1999
Aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups	47	47			1999
55 回会議					
Cinnamyl alcohol and related flavouring agents	55	50	5		2000
Furfuryl alcohol and related flavouring agents	15		9	6	2000
Phenol and phenol derivatives	48	47		1	2000
Pulegone and related flavouring agents	6	2	4		2000
57 回会議					
Pyrazine derivatives	41		32	9	2001
Aromatic substituted secondary alcohols, ketones and related esters	38	28	6	4	2001
Benzyl derivatives	37	37			2001
Hydroxy- and alkoxy-substituted benzyl derivatives	46	36	10		2001
Aliphatic acyclic diols, triols and related substances	31	23	5	3	2001
Aliphatic acyclic acetals	10	10			2001
59 回会議					
Alicyclic primary alcohols, aldehydes acids and related esters	26	26			2002
Phenethyl alcohol, aldehyde, acid and related acetals and esters	43	39		4	2002
Sulfur-containing heterocyclic and heteroaromatic derivatives	30		21	9	2002
Sulfur-substituted furan derivatives	33		18	15	2002
Alicyclic ketones and secondary alcohols	25	6	19		2002
Aliphatic secondary alcohols and ketones	39	11	28		2002

FLAVORING SUBSTANCES EVALUATED BY JECFA USING THE PROCEDURE 1996-2007 (CONT'D)

Flavouring Agents/Group	No. in Group	Structural Class			Year
		I	II	III	
61st Meeting					
Alicyclic, alicyclic-fused and aromatic-fused ring lactones	16	4		12	2003
Aliphatic alicyclic linear α,β -unsaturated, di- and trienals and related alcohols, acids and esters	26	26			2003
Aliphatic branched-chain saturated and unsaturated alcohols, aldehydes, acids and related esters	32	32			2003
Aliphatic and aromatic ethers	29	9	12	8	2003
Hydroxypropenylbenzenes	9	6		3	2003
Linear branched-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, acids and related esters (addendum)	20	20			2003
Simple aliphatic and aromatic sulfides and thiols (addendum)	12	11		1	2003
63rd Meeting					
Pyridine, pyrrole, and quinoline derivatives	22	3	13	6	2004
Aliphatic and alicyclic hydrocarbons	25	22		3	2004
Aromatic hydrocarbons	32	32			2004
Aliphatic, linear α,β -unsaturated aldehydes, acids and related alcohols, acetals and esters	37	37			2004
Monocyclic and bicyclic secondary alcohols, ketones and related esters	32	22	9	1	2004
Amino acids and related substances (<i>not evaluated according to Procedure</i>)	20	19		1	2004
65th Meeting					
Maltol and related substances	7	4		3	2005
Furan-substituted derivatives – <i>NOT EVALUATED</i>	40		30	10	2005
Eugenol and related hydroxyallylbenzene derivatives	7	7			2005
Anthranilate derivatives	19				2005
Miscellaneous nitrogen- containing flavouring agents	16		16		2005
Epoxides	9			9	2005
Aliphatic and aromatic amines and amides	37	16	11	10	2005

この安全性評価手順を用いてJECFAによって評価された フレーバー物質 (1996年から2007年まで)(続き)

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		I	II	III	
61 回会議					
Alicyclic, alicyclic-fused and aromatic-fused ring lactones	16	4		12	2003
Aliphatic alicyclic linear α,β -unsaturated, di- and trienals and related alcohols, acids and esters	26	26			2003
Aliphatic branched-chain saturated and unsaturated alcohols, aldehydes, acids and related esters	32	32			2003
Aliphatic and aromatic ethers	29	9	12	8	2003
Hydroxypropenylbenzenes	9	6		3	2003
Linear branched-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, acids and related esters (addendum)	20	20			2003
Simple aliphatic and aromatic sulfides and thiols (addendum)	12	11		1	2003
63 回会議					
Pyridine, pyrrole, and quinoline derivatives	22	3	13	6	2004
Aliphatic and alicyclic hydrocarbons	25	22		3	2004
Aromatic hydrocarbons	32	32			2004
Aliphatic, linear α,β -unsaturated aldehydes, acids and related alcohols, acetals and esters	37	37			2004
Monocyclic and bicyclic secondary alcohols, ketones and related esters	32	22	9	1	2004
Amino acids and related substances (<i>not evaluated according to Procedure</i>)	20	19		1	2004
65 回会議					
Maltol and related substances	7	4		3	2005
Furan-substituted derivatives – <i>NOT EVALUATED</i>	40		30	10	2005
Eugenol and related hydroxyallylbenzene derivatives	7	7			2005
Anthranilate derivatives	19				2005
Miscellaneous nitrogen- containing flavouring agents	16		16		2005
Epoxides	9			9	2005
Aliphatic and aromatic amines and amides	37	16	11	10	2005

FLAVORING SUBSTANCES EVALUATED BY JECFA USING THE PROCEDURE 1996-2007 (CONT'D)

Flavouring Agents/Group	No. in Group	Structural Class			Year
		I	II	III	
68th Meeting					
Linear and branched-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, acids, and related esters (addendum)	27	27			2007
Aliphatic acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances (addendum)	15	13	2		2007
Simple aliphatic and aromatic sulfides and thiols (addendum)	52	41	6	5	2007
Aliphatic acyclic diols, triols, and related substances (addendum)	15	15			2007
Aliphatic acetals (addendum)	24	24			2007
Sulfur-containing heterocyclic compounds (addendum)	17		10	7	2007
Aliphatic and aromatic amines and amides (addendum)	13	5		8	2007
Aliphatic acyclic linear α,β -unsaturated di- and trienals and related alcohols, acids and esters (addendum)	7	7			2007
Total	1,763	1,246	364	153	

この安全性評価手順を用いてJECFAによって評価された フレーバー物質（1996年から2007年まで）(続き)

フレーバー物質名 / グループ名	グループ 内の物質 数	構造クラス			開催年
		I	II	III	
68 回会議					
Linear and branched-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, acids, and related esters (addendum)	27	27			2007
Aliphatic acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances (addendum)	15	13	2		2007
Simple aliphatic and aromatic sulfides and thiols (addendum)	52	41	6	5	2007
Aliphatic acyclic diols, triols, and related substances (addendum)	15	15			2007
Aliphatic acetals (addendum)	24	24			2007
Sulfur-containing heterocyclic compounds (addendum)	17		10	7	2007
Aliphatic and aromatic amines and amides (addendum)	13	5		8	2007
Aliphatic acyclic linear α,β -unsaturated di- and trienals and related alcohols, acids and esters (addendum)	7	7			2007
計	1,763	1,246	364	153	

SUMMARY OF JECFA'S EVALUATION OF FLAVORING SUBSTANCES BASED ON THE PROCEDURE (1996-2007)

Conclusions of JECFA's Evaluation	No. of Flavouring Substances
No Safety Concern	1,570
Not Evaluated	51
Evaluation Tentative Pending Submission of Intake Data	142
Total	1,763

JECFA 2008: 105 Flavoring substances will be evaluated

この手順に基づく JECFAのフレーバー物質評価結果概要 (1996-2007)

JECFA 評価における結論	フレーバー物質の数
安全性の懸念無し	1,570
評価されず	51
摂取量データの提出まで評価結果は暫定とする	142
計	1,763

2008年JECFA会議: フレーバー物質は105物質が評価予定

CONCLUSIONS

- **The procedure provides a safety evaluation method for flavoring substances which uses available data on metabolism, toxicity, and intake;**
- **Integrates data on intake, chemical structure, metabolism and toxicity consistent with JECFA principles;**
- **Identifies substances for which the intakes are not a safety concern - and those requiring further evaluation;**
- **Has provided a simplified, structured and methodical approach for the safety assessment of 1,763 flavoring substances.**

結論

- この手順は、入手できる限りの代謝、毒性、及び摂取量のデータを用いて、フレーバー物質の安全性を評価する方法を提供するものである。
- JECFAの原則と矛盾がない形で摂取量、化学構造、代謝、及び毒性に関するデータを統合するものである。
- その摂取量のもとでは安全性に懸念のないと考えられる物質と、更なる評価が必要な物質を見分けるものである。
- 単純化された、構造的かつ整然としたアプローチを提供し、これまでに、1763のフレーバー物質が安全性評価されている。