1)

内分泌撹乱化学物質のリスク評価と、不確実性分析

関沢　純　国立医薬品食品衛生研究所
化学物質情報部

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2)

環境ホルモンについて問題になっている事柄

多様性：エンドポイント、化合物の種類、生物種、活性の強度

影響の性質：次世代への影響、直接毒性でなく引き金的効果

試験管内データの意味合い：ヒト、生物でどうか

ハザードとリスク：毒性データのみ、曝露データのみでは
リスクはわからない

データ、知識のギャップと不確実性：

3)

わからないことへの不安

一般市民の間でダイオキシンや環境ホルモンなど化学物質の有害影響について、わからないことからくる不安が大きい。

この中には

（1）化学物質の名前を聞いてもどのような有害影響を及ぼす可能性があるか理解できない不満

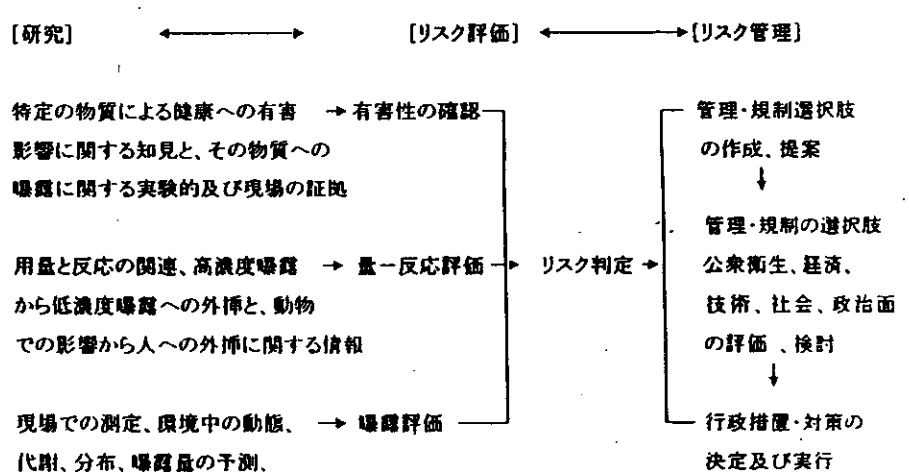
（2）わかっていることを十分知らされていないのでないかという不信

（3）週刊誌などによるセンセーショナルな報道に対し本当のところはどうなのか知りたいという要求

（4）詳細は理解できないけれども、とにかく有害な影響をできる限り少なくして欲しいという要望

などが混在している。リスクを管理する立場にある者と、リスクを受ける可能性を持つ人々の間の適切なリスクについてのコミュニケーションのあり方が問題となっている

4)



米国科学審議会のリスク評価の枠組み（1983）

5)

科学的推測
科学的な証拠と合理的な仮定に基づき、危害の起こりやすさや程度を、ある範囲の不確実さを許容しつつ、いつ、誰に、どのような危害がおきるかを推測

価値判断
知識や経験、立場、時には信念に根ざしており異なる答えが生じうる人のリスクの認知、受容を左右する要因

仮定の立て方や予測の道筋の明示と批判的検討

違いの尊重とその理由や原因の相互理解

リスク対応の意思決定

6)

＊＊＊推測の必要性と不確実性の内容＊＊＊

生体と、それを取り巻く環境のそれぞれについて複雑な要因が絡み合い作用しあっているので、データの取得において、以下のような理由から推測が必要になる

(1) 人に関するデータの取得は実際的に不可能な場合がある。
(2) 実験や調査において、さまざまの条件についての測定および実験データを十分そろえるには困難が伴う。
(3) メカニズムの未解明などのため、理論が未完成である。
(4) 生物個体の性質と影響の受け方、環境条件は均一でなく、ある分布を持っている。

関沢（1997）「情報の検策と評価」、化学物質のリスクアセスメント（現状と問題点）、薬業時報社 pp. 15-30

7)

情報における不確実性とリスク評価の関係

評価に必要な情報が十分にない、作用メカニズムについて科学的に未解明の部分がある、などの不確実性要因

情報と科学の不備を補うための適切な仮定と推論の設定
不確実な箇所の明示、例えばリスク評価に
(1) どのような情報が今後必要とされ
(2) 不確実性を含む情報の内容、性質と評価結果の信頼度はどのような関係にあるか、など

入手可能なデータと仮定に基づく現時点での科学的な結論

現時点での安全対策の選択と長期的対策の指針および戦略の設定

関沢（1997）「情報の検策と評価」、化学物質のリスクアセスメント（現状と問題点）、薬業時報社 pp. 15-30

8)

リスク評価における不確実性分析

真の不確実性＝True Uncertainty

(1) 仮説、外挿やモデルにおける構造的な、あるいはメカニズムの未解明など知識の不十分さによる不確実性

(2) 測定における試験動物やサンプルの扱いの違いや誤差による不確実性

→ 不確実性の内容を分析し、何が大きく寄与しているかを指摘し必要な研究を進め不確実性を減らすことが可能

分布の幅（ばらつき）があり値が定まらない不確実性＝Variability

(3) 生物の体重、感受性などにばらつきがあり、曝露のレベルでも ばらつきがあり固有な分布を示すことによる不確実性

→ ばらつきに分布のかたちを的確に推測することでリスク評価の信頼性を高めることが可能

9)

$$ADI = \frac{NOAEL}{Safetyfactor}$$

Safety factor (安全係数) = Uncertainty factor (不確実性係数)

10)

Threshold Effects の評価法

NOAEL（無毒性量）の評価に影響する要素
・動物の種、系、性　・実験の規模、期間
・測定、観察項目　・用量設定

UF（不確実因子）の内容
10:動物とヒトとの種差
10:一般のヒトと高感受性グループとの差
その他：最大100を用いる。
・LOAELに対しては 3, 5または10
・毒性の質に対しては～10
・不十分なデータに対しては～10

11)

CASES WHEN SAFETY FACTORS OTHER THAN 100 WERE APPLIED BY THE JMPR
(EXCEPT EVALUATIONS BASED ON HUMAN DATA)

Pesticide	ADI (mg/kg bw)	Animal species	NO(A)EL (mg/kg bw)	Type of test or duration of exposure	Safety factor	Year of evaluation	Grouping *
ISOFENPHOS	0.001	RAT	0.05	2 Years	50	1986	
	0.001	DOG	0.05	2 Years	50	1986	
ABAMECTIN	0.002	RAT	0.12	2 Generations	60	1997	4
	0.002	DOG	0.25	1 Year	125	1997	
AMITROLE	0.002	DOG	0.29	1 Year	150	1997	
	0.002	RAT	0.12	2 Generations	60	1997	4
	0.001	RAT	0.1	90 Days	50	1997	4
FENVALERATE	0.02	MOUSE	3.5	87 OR 91 Weeks	175	1986	
FENTIN COMPOUNDS	0.0005	RAT	0.1	2 Years	200	1991	3
	0.0005	RABBIT	0.1	Maternal	200	1991	3
PHOSALONE	0.001	RAT	0.2	2 Years	200	1993	3
TEFLUBENZURON	0.01	MOUSE	LOAEL 2.1	18 Months Carcinogenicity study	210	1994	2
ALDRIN	0.0001	RAT	0.025	2 Years	250	1994	4
DIELDRIN	0.0001	RAT	0.025	2 Years	250	1994	4
HEPTACHLOR	0.0001	DOG	0.025	Reproduction	250	1994	1
	0.0001	DOG	0.025	2 Years	250	1994	1
METHOPRENE	0.1	RAT	25	2 Generations	250	1987	1
LINDANE	0.001	RAT	0.5	2 Years	500	1997	3
DIMETHOATE	0.002	RAT	1.2	Reproduction	600	1996	3
TECNAZENE	0.02	DOG	15	90 Days	750	1994	1
ZIRAM	0.003	RAT	LOAEL 2.5	2 Years	830	1996	2
PROPYRENETHIOUREA	0.0002	MOUSE	0.2	Long term	1000	1993	1
CARBARYL	0.003	MOUSE	LOAEL15	2 Years	5000	1996	1,2,3
DINOCAP	0.001	DOG	0.4	2 Years	100<	1989	3
	0.001	RABBIT	0.5	Teratology	100<	1989	3
FERBAM see ziram	0.003	RAT	12	2 Years		1996	2

* Grouping based on the reasons to choose safety factors other than 100
1: Insufficient data
2: ADI estimated on LOAEL, not NOAEL
3: Concern on specific toxicity
4: Species variability

12)

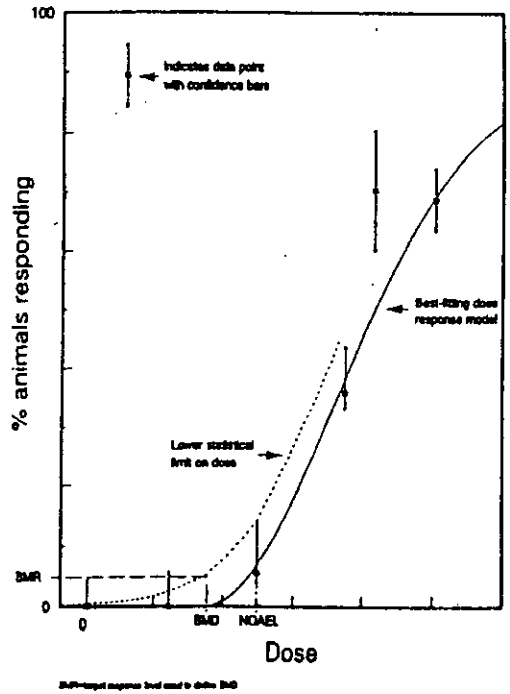


Figure 1. Example of calculation of a BMD

13)

大豆製品からの日本人のイソフラボノイド摂取量
(Reinli & Block, 1996; Franke et al., 1994; Toda et al., 1997; 厚生省，1996より計算)

大豆と大豆製品	日本人の摂取量 (g)	ダイゼインの含量 μg/g 平均 (範囲)	ダイゼインの推定摂取量(mg)
豆腐	35.7	99 (32-146)	3.5
味噌	14.0	187 (71-366)	2.6
大豆	2.3	697 (22-1,915)	1.6
納豆	4.9	267(199-354)	1.3
油揚げなど	8	148(74-187)	1.2
合計	64.9		10.2

大豆と大豆製品	日本人の摂取量 (g)	ゲニステインの含量 μg/g 平均 (範囲)	ゲニステインの推定摂取量(mg)
豆腐	35.7	169 (86-306)	6.0
味噌	14.0	247 (149-524)	3.5
大豆	2.3	965 (200-1,897)	2.2
納豆	4.9	403(374-506)	2.0
油揚げなど	8	215(185-228)	1.7
合計	64.9		15.4

＊日本人の大豆と大豆製品平均摂取量は、64.9 gである
＊ｲｿﾌﾗﾎﾞﾉｲﾄﾞ摂取量の概算は、10.2 mg (ﾀﾞｲｾﾞｲﾝ) + 15.4 mg (ｹﾞﾆｽﾃｲﾝ) = 25.6 mg
＊体重55kgとして、ﾀﾞｲｾﾞｲﾝ 185μg/kg体重，ｹﾞﾆｽﾃｲﾝ 280μg/kg体重の摂取量になる

14)

大豆製品からの日本人のイソフラボノイド摂取量

Isoflavonoid Intake of Japanese from Soybean Products

(Reinli & Block, 1996; Franke et al., 1994; Toda et al., 1997; 厚生省，1996より計算)

大豆と大豆製品	日本人の摂取量 (g)	ダイゼインの含量, 平均	ゲニステインの含量, 平均
豆腐	35.7	99 μg/g	169 μg/g
味噌	14.0	187 μg/g	247 μg/g
大豆	2.3	697 μg/g	965 μg/g
納豆	4.9	267 μg/g	403 μg/g
油揚げなど	8	148 μg/g	215 μg/g
合計	64.9	10.2 mg	15.4 mg

15)

血漿中のイソフラボノイドの濃度
ISOFLAVONOIDS IN PLASMA
日本人男性とフィンランド人男性の比較 (Adlercreutzら、1993)
Comparison between Japanese Male and Finnish Male (Adlercreutz et al., 1993)

イソフラボノイド Isoflavonoid	幾何平均 (95%信頼限界): n mol/L Geometric mean (95% C.L.) 日本人男性 (n = 14) Japanese Male	フィンランド人男性 (n = 14) Finnish Male	比率: Ratio Japanese/Finnish
ダイゼイン Daidzein			
遊離+硫酸抱合体: Free + Sulfate	12.8 (6.0-27.4)	0.6 (0.4-1.0)	-
グルクロン酸抱合体: Glucuronide	91.8 (40.4-211)	2.0 (1.1-3.7)	-
合計 Total	107 (47.4-237)	6.2 (3.9-10.1)	17.3
ゲニステイン Genistein			
遊離+硫酸抱合体: Free + Sulfate	7.8 (3.2-19.1)	0.5 (0.2-1.1)	-
グルクロン酸抱合体: Glucuronide	167 (72.2-388)	5.3 (3.2-8.9)	-
合計 Total	276 (116-652)	6.3 (3.3-14.6)	43.8
イクオール Equol			
遊離+硫酸抱合体: Free + Sulfate	0.6 (0.1-3.0)	0.1 (0-0.2)	-
グルクロン酸抱合体: Glucuronide	3.9 (0.8-18.2)	0.4 (0.1-1.7)	-
合計 Total	5.5 (1.4-22.0)	0.8 (0.3-2.2)	6.9

16)

植物ホルモンと乳がんの症例ー対照研究
Odds Ratios for Breast Cancer Risk Associated with Intake of Phytoestrogens (Ingram et al., 1997)

	尿中排泄量 (nmole/24h) Urine excretion	対照人数 Control #	症例人数 Case #	補正後オッズ比 (95%信頼限界) Adjusted Odds Ratios (95% C.L.)	
ダイゼイン*1 Daidzein	≦600	51	31	1.00	
	<600 - ≦900	29	38	0.60	↓
	<900 - ≦1300	29	35	0.60	↓
	1300<	24	32	0.47	↓↓
イクオール*2 Equol	≦70	47	35	1.00	
	<70 - ≦110	37	37	0.45	↓
	<110 - ≦185	35	36	0.52	↓
	<185	24	36	0.27	↓↓
エンテロラクトン*3 Enterolactone	≦1450	51	36	1.00	
	<1450 - ≦3100	44	36	0.81	↓
	<3100 - ≦5250	30	36	0.65	↓
	<5250	19	36	0.36	↓↓
マタイレシノール Metairesinol	≦17	30	37	1.00	
	<17 - ≦30	45	36	2.38	↑↑
	<30 - ≦42	31	32	1.98	↑
	<42	38	39	2.16	↑↑

*1 日本人女性の平均は、(Average for Japanese women) : 2560 nmole/24h
*2 日本人女性の平均は、(Average for Japanese women) : 562 nmole/24h
*3 日本人女性の平均は、(Average for Japanese women) : 890 nmole/24h
*1-3 : Adlercreutz et al. (1991)

17)

閉経前の女性へのイソフラボノイド投与による
性周期への影響　Cassidyら,1995より

	生理周期(日)	卵胞期(日)
イソフラボノイド抱合体 45mg投与	29.0	17.5
対照	27.5	15.0
遊離イソフラボノイド 25mg投与	30.7	25.3
対照	19.0	16.0
イソフラボノイドフリー 大豆製品投与	29.0	17.0
対照	29.0	17.0
イソフラボノイド抱合体 23mg投与	32.0	21.0
対照	33.0	21.0

18)

大豆たんぱく摂取の血清脂質への影響:
38例の臨床試験結果のメタアナリシス(Andersonほか, 1995)

	平均 (割合)	95%信頼限界または範囲
大豆たんぱく摂取量	47 g	17 - 124 g
全コレステロール値の低下	23.2 mg/dl (9.3%↓)	13.5 - 32.9 mg/dl
初期値*が中程度のグループ (127.1-197.8 mg/dl)	5.2 mg/dl (3.3%↓)	-6.7 - 17.1 mg/dl
初期値*がやや高いグループ (201.2-255.4 mg/dl)	10.1 mg/dl (4.4%↓)	-1.7 - 21.8 mg/dl
初期値*が高いグループ (259.3-332.8 mg/dl)	22.2 mg/dl (7.4%↓)	7.1 - 37.3 mg/dl
初期値*が非常に高いグループ (335 mg/dl以上)	71.5 mg/dl (19.8%↓)	56.5-88.6 mg/dl
低比重リポたんぱくコレステロールの低下	21.7 mg/dl (12.9%↓)	11.2 - 31.7 mg/dl
初期値*が中程度のグループ (127.1-197.8 mg/dl)	7.1 mg/dl (7.7%↓)	-6.0 - 20.0 mg/dl
初期値*がやや高いグループ (201.2-255.4 mg/dl)	10.7 mg/dl (8.8%↓)	-2.9 -24.3 mg/dl
初期値*が高いグループ (259.3-332.8 mg/dl)	18.3 mg/dl (9.8%↓)	1.3 - 35.3 mg/dl
初期値*が非常に高いグループ (335 mg/dl以上)	88.1 mg/dl (24.0%↓)	45.9 - 90.2 mg/dl
トリグリセライドの低下	13.3 mg/dl (10.5%↓)	0.3 -25.7 mg/dl
高比重リポたんぱくコレステロールの増加	(2.4%↑)	

*全コレステロール値の初期値により4分位毎に分けた

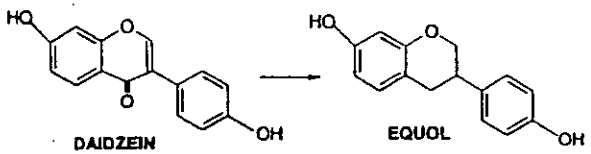
Lovatiら(1987)によると、大豆たんぱくを摂取したヒトはそうでないヒトに比べて、単球の低比重りぽたんぱく受容体の活性が8倍になった。
さるを用いたAnthonyら(1995)の研究によれば、コレステロール低下の原因の60-70%は大豆中のエストロゲンによって説明可能である。

19)

日本人のイソフラボノイドの尿中排泄量の個人差

Adlercreutz et al. Am J Clin Nutr Vol. 54: 1093-1100, 1991;

Subject, sex, age	Daidzein	Equol	Genistein	Total isoflavonoids
1 Male 26 year	3.38	9.16	7.99	20.76
2 Male 41 year	5.25	6.15	15.52	27.04
3 Female 30 year	1.25	3.28	1.85	6.6
4 Male 6 year	2.15	0.85	3.41	6.93
5 Female 42 year	2.2	0.16	3.55	7.07
6 Male 38 year	1.6	0.07	4.93	6.99
7 Male 8 year	3.02	0.02	4.8	8.64
8 Male 7 year	3.23	0.01	5.66	8.97
9 Female 33 year	3.11	0.01	4.48	8.58
Average	2.8	2.19	5.8	11.29



20)

食物中の植物エストロゲンの抗がん、および抗心疾患作用

抗がん作用の機作

- 弱いエストロゲン作用
- 抗酸化作用
- チロシンキナーゼ阻害と、転移と浸潤の阻害作用
- 血管腫の阻害

抗心疾患作用の機作

- 弱いエストロゲン作用（血清脂質組成の改善）
- 抗酸化作用（低比重リポたんぱくコレステロールのの酸化的障害の阻害）
- チロシンキナーゼ阻害（血小板由来成長因子ほかによる動脈硬化過程の阻害、トロンビンによる血小板凝集の阻害など）

21)

内分泌撹乱化学物質(ED)のリスク分類スキーム

目的

データギャップを確認する

リスク管理の優先順位付けの参考にする

22)

内分泌撹乱化学物質のリスクに基づく分類の試み

Class A　Probabale Risk to Humans（懸念すべきレベル）

影響レベル、曝露レベル、メカニズムのデータと、データの信頼度についての証拠を総合すると、曝露される人の条件によっては、リスクが懸念される

Class B　Possible Risk to Humans（可能性レベル）

影響レベル、曝露レベル、メカニズムのデータと、データの信頼度についての証拠を総合した時に、確定的といえないが曝露される人の条件によっては、リスクを懸念する必要がある

Class C　No Existing Risk to Humans（安全レベル）

影響レベル、曝露レベル、メカニズムのデータと、データの信頼度についての証拠を総合した時に、現時点では人に対するリスクを懸念する必要はない

Class D　Unclassifiable Reagrding Risk To Humans

（分類不能レベル）

影響レベル、曝露レベル、メカニズムのデータと、データの信頼度についての証拠を総合した時に、現時点で判断をいずれかのくだすには不十分である

23)

内分泌撹乱化学物質（ED）のリスク分類スキーム

EDの可能性なし（例：高分子量物質） Yes ⟶ Class C (No Risk)

No

↓

EDとしての影響/曝露データがある No ⟶ Class D (Unclassifiable)

Yes　Yes　（データ内容の確認）

↓

EDとしての陽性データ(in vitro/QSAR) No ⟶ Class C (No Risk)

Yes/ambiguous

↓

EDとしての陽性データ(in vivo/dose-response) No ⟶ Class C (No Risk)

Yes　or Class D (Unclassifiable)

↓

Dose-response データが人にあてはまる　No ⟶ Class C(No Risk)

Yes

↓

人の曝露の可能性(NOAEL/LOAEL/UF) No ⟶ Class C (No Risk)

Yes

↓

Class A (Probable) or B (Possible)　：　証拠の確かさによる

Uncertainty analysis in human effects assessment

Theo Vermeire
National Institute of Public Health and the Environment
February 26, 1999

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TNO: Betty Hakkert Monique Rennen, Hantzen Stevenson

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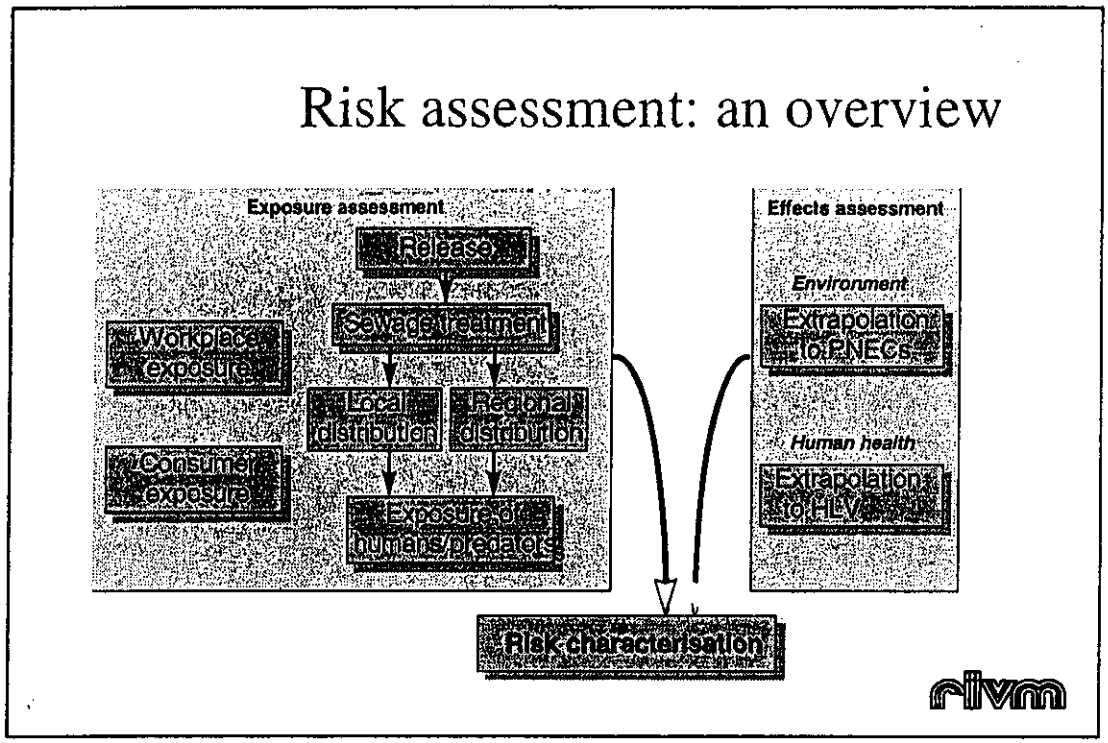
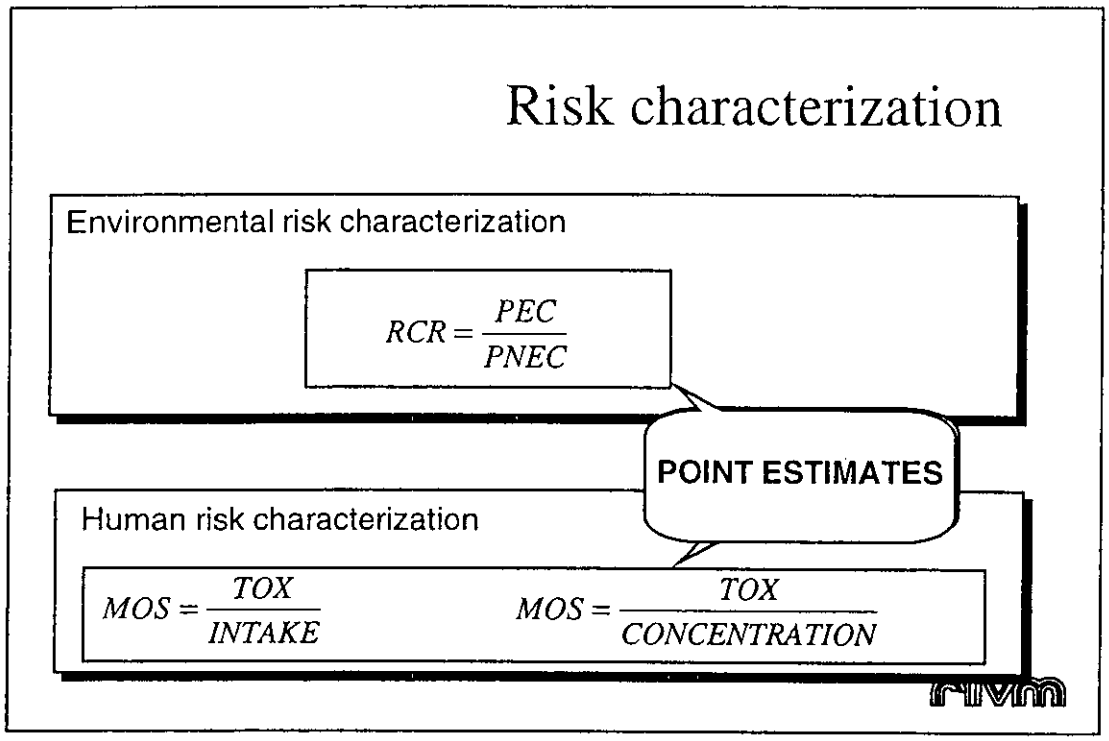
The general goal of this discussion paper is to contribute towards further harmonization of the human health risk assessment. First, it discusses the development of a formal, harmonized set of assessment factors. The status quo with regard to assessment factors is reviewed: i.e.. the type of factors to be identified, the range of values assigned as well as the presence or absence of a scientific basis for these values. Options are presented for a set of default values and probabilistic distributions for assessment factors based on the state of the art. Methods of combining default values or probabilistic distributions of assessment factors are also described. Secondly, the effect parameter, the No-Observed-Adverse-Effect Level (NOAEL), is discussed. This NOAEL as selected from the toxicological database may be a poor substitute for the unknown, true No-Adverse-Effect level (NAEL). New developments are presented with regard to the estimation of the NAEL. Finally, a strategy is proposed for implementation of the new developments into human health risk assessments.

This work is a collaboration between TNO (Nutrition and Food Research Institute) and RIVM (National Institute of Public Health and the Environment).



Shown is the EU(European Union) Risk Assessment scheme for new and existing substances. The risk assessment methodology is laid out in Technical Guidance Documents and implemented in a PC-program EUSES European Union System for the Evaluation of Substances).



The measure of risk RCR (Risk Characterization Ratio) often is a point estimate: e.g.. PEC/PNEC for the environment (Predicted Environmental Concentration/Predicted No-Effect Concentration) and a MOS (Margin of Safety) for human populations.

TOX = Toxicity parameter such as the NOAEL (No-Observed-Adverse-Effect Level) of LOAEL (Lowest-Observed-Adverse-Effect Level)

INTAKE = a measured or predicted daily exposure dose which can be taken up via the skin or orally

The MOS is evaluated taking into account all uncertainties (intraspecies, interspecies, route-to-route, subchronic to chronic, LOAEL to NOAEL, inadequacies in database). At this point in time there is no harmonization at international/EU level with regard to quantification of uncertainties(extrapolation/assessment factors).

Disadvantages of point estimates

(Thompson & Graham, Hum. Ecol. Risk Assessm. 2: 1008-1034)

1. It is generally not possible to determine precisely where a point estimate lies in the range of possibilities.
2. Use of point estimates may mislead risk managers by producing falsely precise estimates.
3. Use of point estimates may lead to non-optimal decisions.
4. Use of point estimates eliminates the incentives for conducting research that might reduce uncertainty.
5. Use of point estimates ignores variability in the population and thus precludes discussion and consideration of inequity in the distribution of risk in the exposed population.

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This sheet highlights disadvantages of the use of point estimates for risk characterization.

Uncertainty =

1. Uncertainty due to natural variability in time or space. Uncertainty caused by variability cannot be reduced by further research.

2. Uncertainty due to ignorance.

3. Uncertainty due to error.

4. Uncertainty due to choices

Advantages of probabilistic RA

Burmaster, Hum.Ecol. Risk Assess. 2:25-29

The probabilistic framework of risk (Burmaster, 1996):

1. Honours the definition of risk.
2. Includes all information available about uncertainty and variability inherent in the assessment.
3. Reveals the compounded conservatism in the deterministic framework. Risk managers and the general public can see the full range of possibilities.
4. Reveals the nature and the extent of professional judgement in a risk assessment.
5. Can indicate the main sources of uncertainty in the final result, thereby offering an efficient way to refine the assessment.
6. Re-establishes the now blurred boundary between risk assessment and risk management. Too often risk assessors use exaggerated point values so the risk manager can ignore the complexities and cost-effectiveness of measures. Allows the risk manager to make a trade-off between the costs of type I errors (rejecting a harmless substance) and type II errors (accepting a harmful substance).
7. Ultimately saves money as the results are generally less conservative, yet fully protective.
8. Is closer to the truth. The output is a distribution of potential risk. Getting closer to the truth is preferable to the world of fiction created when distributions are replaced by single numbers.

And additionally:

9. Allows for comparing chemicals with different degrees of uncertainty.
10. Acts to reward the input of measured data. Even when additional data lead to higher PEC/PNEC ratios, their uncertainty may be lower which may therefore result in an assessment with greater confidence.

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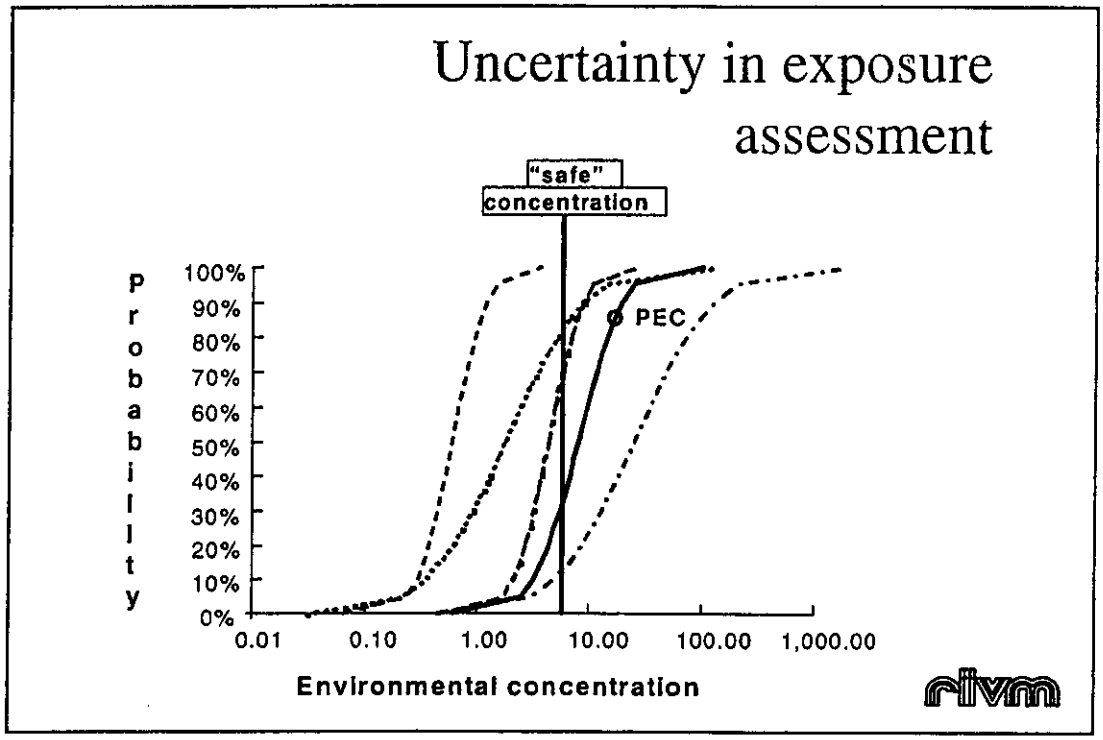
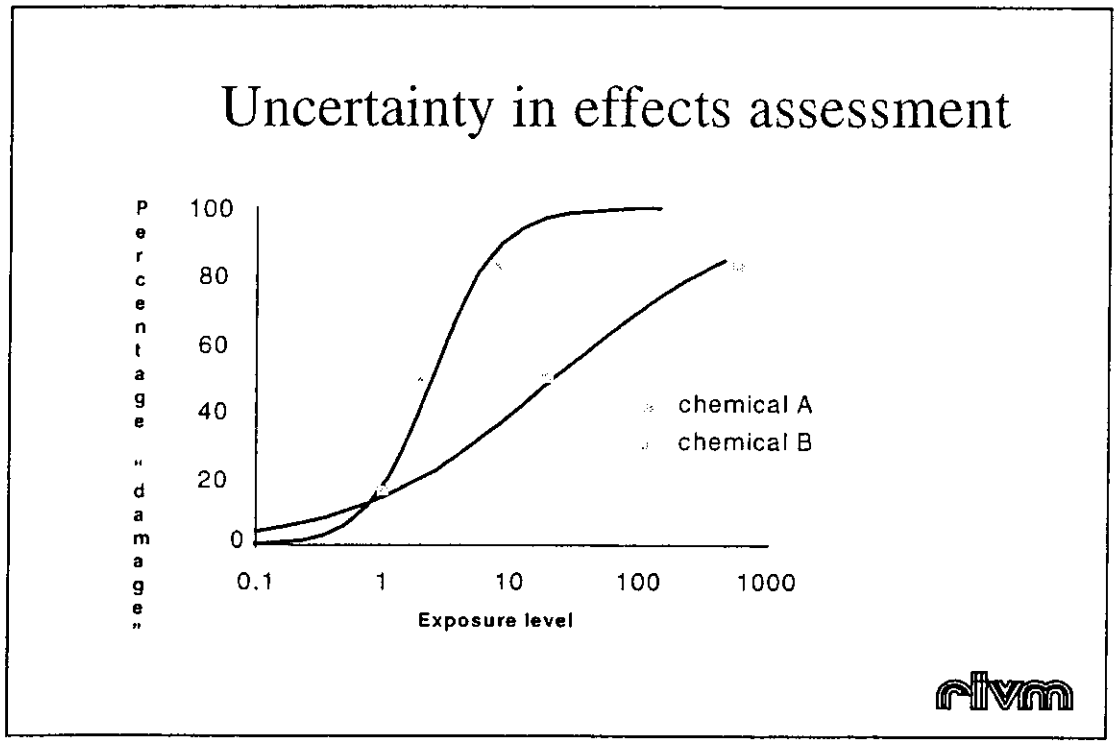
This sheet highlights the advantages of probabilistic risk assessment.



Example od uncertainty analysis in exposure assessment. The PEC is the point estimate of exposure. Alternatively this PEC could be a predicted dose.The PEC shown is on the "unsafe" side. Due to uncertainty there is a 30% probability that the PEC is "safe". Environmental variability is represented by alternative distributions.



We cannot usually estimate a risk because impacts are not properly defined. Currently a no-effect level is estimated by applying assessment factors (10 - 1000) on the results of laboratory tests. The impact of exceedance of this safe level remains unknown. The diagram shows the desired result of risk assessment as a hypothetical fraction of the population (humans) or species (environment) which is exposed above their no-effect level. This result can be achieved by taking uncertainty and variability into account as will be discussed further in this presentation.

Disadvantages

Table 1 Disadvantages or costs of probabilistic risk assessment.

Explanations for the limited use of probabilistic risk assessment (Thompson & Graham, 1996):

1. Lack of (EPA) guidance.
2. The existence of established point estimates for some inputs (e.g., the Exposure Factors Handbook).
3. Inexperience with using probabilistic results.
4. Increased legal challenge.
5. Mistrust and suspicion. Risk managers may suspect that outcome will favour industry (perhaps just by delaying decisions by endless discussion) or may be worried that the assessment contains hidden assumptions or hard-to-detect errors.
6. Difficulties in risk communication.

Costs of probabilistic risk assessment (Burmaster, 1996):

1. Probabilistic methods need more measured data to estimate the variability or uncertainty in a stochastic variable.
2. Probabilistic methods need many input distributions.
3. To work in the probabilistic framework, risk assessors, toxicologists and regulators need to learn new skills. It takes serious study to learn how to develop, manipulate, and interpret stochastic variables and equations.
4. Risk management decisions are harder to make. The risk manager must consider the character, location, and spread of the whole distribution of risk.
5. Risk communication hinges on the continued development of visual and graphical tools to convey the results.
6. Risk assessors must make sure that guidance manuals do not impede the growth and advancement of their discipline.

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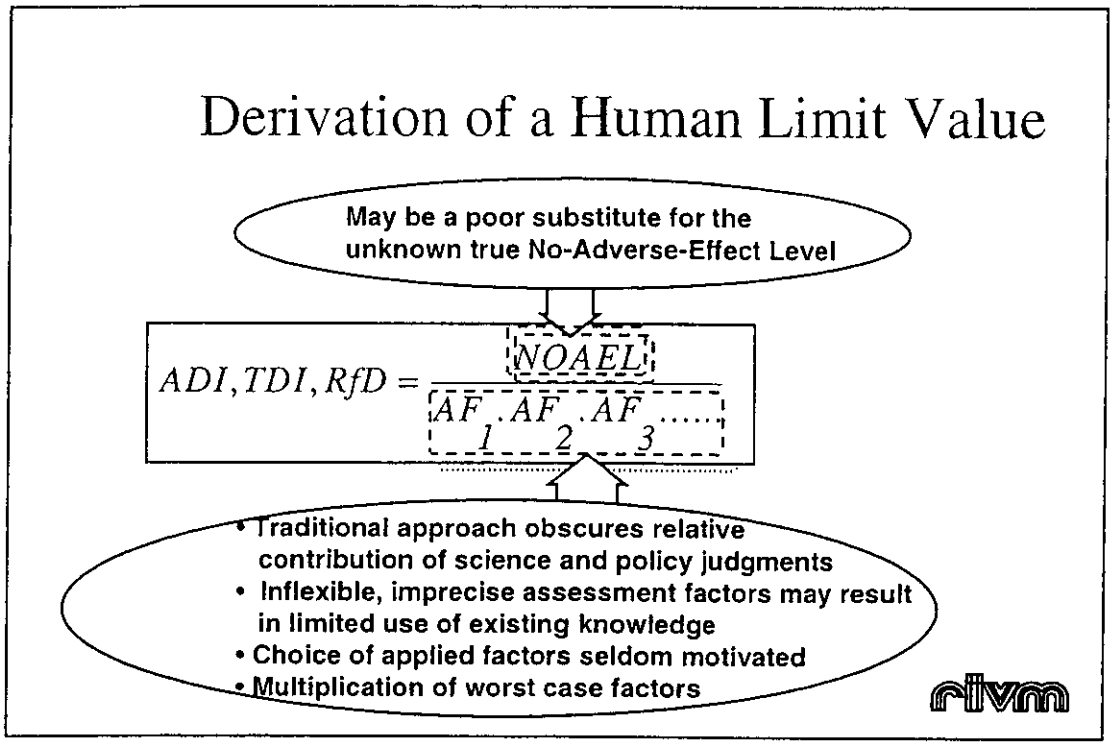
This sheet summarize disadvantages or costs of probabilistic risk assessment.

Risk assessors and managers should discuss advantages and disadvantages to come to a decision on implementation of such methods.It must be demonstrated how decision making can benefit from the extra effort needed to perform probabilistic risk assessment.



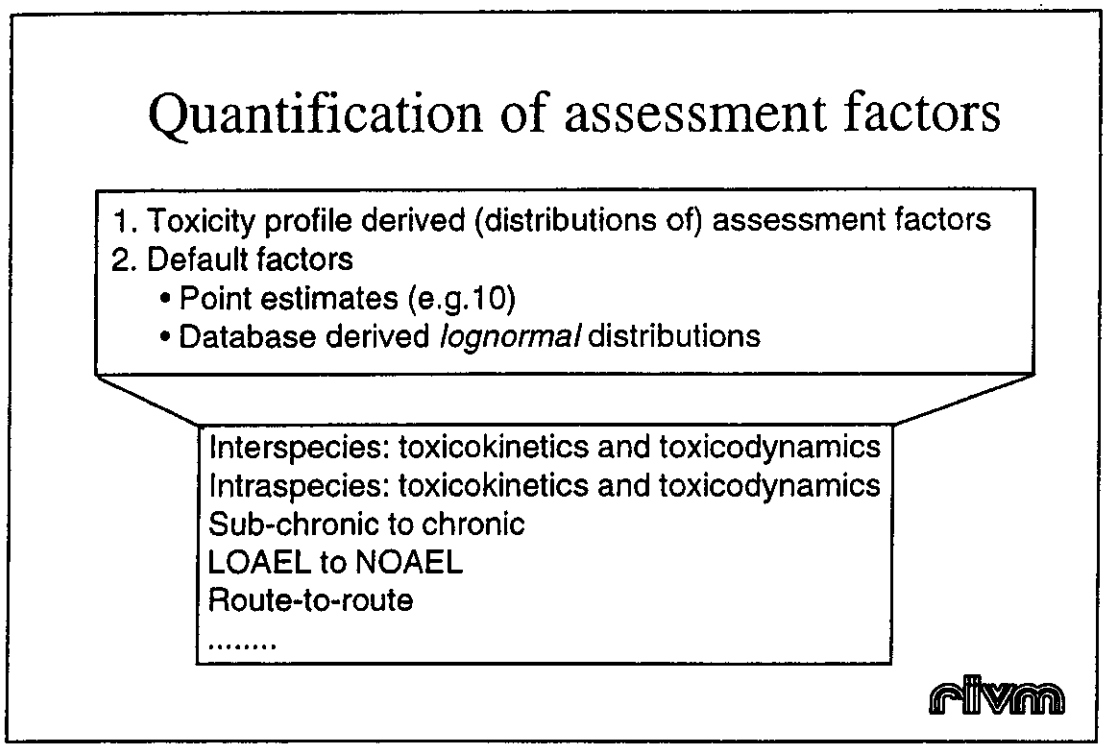
The classical derivation of Human Limit Values (HLVs) such as Acceptable Daily Intakes (ADI), Tolerable Daily Intakes (TDI) and Reference Doses or Concentrations (RfD, RfC) has several shortcomings.

Assessment factors

Few approaches are based on scientific data, but most methods basically rely on the arbitrary imprecise 100-fold factor used to derive the Acceptable Daily Intake (ADI).

The NOAEL

The NOAEL selected from the toxicological database may be a poor substitute for the unknown, true NAEL..



Toxicity derived (distributions of) assessment factors are always preferred above default factors.

With regard to default factors it is recommended to investigate the probabilistic nature of assessment factorsby trying to describe their entire distribution.

Lognormality is assumed for these distributions (based on empirical evidence and on theoretical grounds)

Interspecies factor: scaling

$$Y = aW^n$$

Y = physiological/toxicological characteristic
a = constant
W = body size (weight, surface area)
n = 1 (BW) or 0.75 (caloric demand), 0.67 (surface area)

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For extrapolation of data from animal studies to humans account should be taken of species-specific differences between animals and humans. These interspecies differences can be divided in differences in metabolic size and remaining species-specific differences. To account for differences in metabolic size three methods are used in practice: extrapolation based on body weight, surface area, and caloric demand. These methods can be described by an allometric equation: for that purpose body weight has to be raised to the power 1, 0.67, and 0.75, respectively.

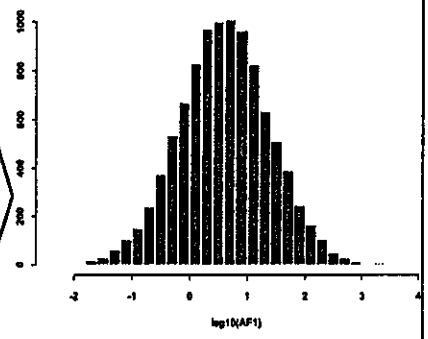
For inhalation NOAELs for systemic effects no correction is made for differences in metabolic size, because extrapolation is already based on toxicological equivalence of a concentration of a substance in the air; animals and humans breath at a rate depending on their caloric requirements

Interspecies 2

Table 7: Distribution parameters derived from the NOAEL ratios

Ratio	N	GM	GSD	P_{90}	P_{95}
$NOAEL_{rat}$ / $NOAEL_{dog}$ (oral, unadjusted)	63	1.3	5.1	10.4	18.8
$NOAEL_{rat}$ / $NOAEL_{dog}$ (oral, adjusted)	63	0.5	5.1	3.6	6.6
$NOAEL_{mouse}$ / $NOAEL_{rat}$ (oral, unadjusted)	67	4.2	5.7	39.3	73.9
$NOAEL_{mouse}$ / $NOAEL_{rat}$ (oral, adjusted)	67	2.4	5.7	22.5	42.2
$NOAEL_{mouse}$ / $NOAEL_{dog}$ (oral, unadjusted)	40	6.4	6.1	64.7	124.6
$NOAEL_{mouse}$ / $NOAEL_{dog}$ (oral, adjusted)	40	1.3	6.1	12.9	24.9
$NOAEL_{mouse}$ / $NOAEL_{rat}$ (respiratory)	21	3.1	7.8	43.6	91.8

N = number of ratios
GM = geometric mean
P_{95} = 95th percentile
GSD = geometric standard deviation
P_{90} = 90th percentile



GM = 4
GSD = 6
P73 = 12 (rat)
P95 = 76 (rat)

To account for the remaining interspecies uncertainties usually a default factor is used. In theory, the remaining uncertainty could be assessed by comparing NOAELs in test animals with estimates of human NOAELs. However, in practice, such an assessment must rely on data from studies derived experimentally for the same substance in different animal species because human data are lacking. The degree of remaining interspecies uncertainty may be obtained by examining the differences (ratios) of the NOAELs established for the same substance in different species. The actual uncertainty in extrapolating from animals to humans is likely to be at least as large as the uncertainty in extrapolating among mice, rats, and dogs.

The ratios (both adjusted and unadjusted for metabolic size) were evaluated by examining their distributions

Interspecies: other examples

	GM	GSD	P95	
Our example:	4	6	76	database-derived
Baird et al., 1996[1]	5.8	4.9	79	database derived
Slob & Pieters, 1998[2]	5	1.3	10	assumption(P99)
Swartout et al., 1998[3]	1+2.1	2	10	assumption
Price et al., 1997[4]	1+2.1	2	10	assumption

1 Hum. Ecol. Risk Assessm. 2: 79-102
2 Risk Analysis 18: 787 - 798
3 Risk Analysis 18: 271 - 282
4 Risk Analysis 17: 427 - 437

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Various proposal on distributions show that still a lot of work and harmonization efforts are needed.