European Food Safety Authority

FSCJ 10th Anniversary Conference "*New Trends in Research on Food Safety Assessment*"

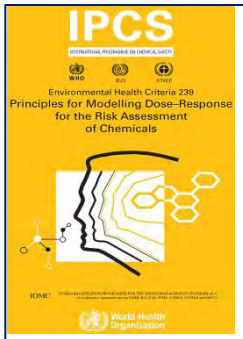
The Margin of Exposure (MOE) Approach

Josef Schlatter

Overview

- **Introduction:** The Risk Assessment Paradigm
  Traditional Food Safety Assessment
  Problematic areas in Risk Assessment
- Issues with genotoxic and carcinogenic compounds
- Dose-response analysis
- The Margin of Exposure Approach
- Examples
- Discussions

EFSA JOURNAL
http://www.efsa.europa.eu/en/publications.htm



Environmental Health Criteria 239
Principles for Modelling Dose–Response for the Risk Assessment of Chemicals

Environmental Health Criteria 240
Principles and Methods for the Risk Assessment of Chemicals in Food

http://www.who.int/foodsafety/chem/principles/en/index1.html

Chemicals in Food and Feed

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Natural constituents

additives

pesticides

Food processing

animal drugs

packaging materials

biotech-nology

Environmental contaminants

overfeeding, deficiencies

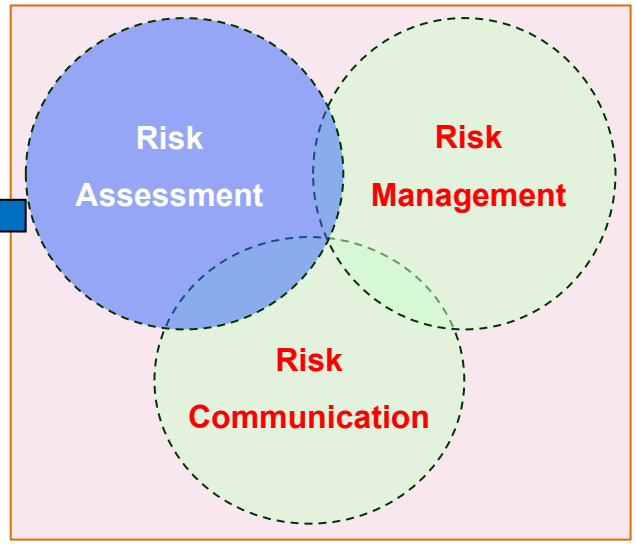
nutrients

Dietary fibers…

Risk assessment paradigm

Hazard characterisation (dose-response)

Hazard identification



Risk characterisation

Exposure assessment

-The large portion size-
Is the 400 g too much or maybe too little ???

EHC 240: http://www.who.int/foodsafety/chem/principles/en/index1.html

Traditional Food Safety Assessment

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Mode of Action	Thresholded	Non-Thresholded Genotoxic Compound
Type of RA	Non-Quantitative Risk Assessment	None
Approach	NOAEL and Safety Factors	Unwanted in Food
Outcome	Intake with no appreciable effects e.g. ADI	ALARA Principle: as low as reasonably achievable

Extrapolation from Animals to Man

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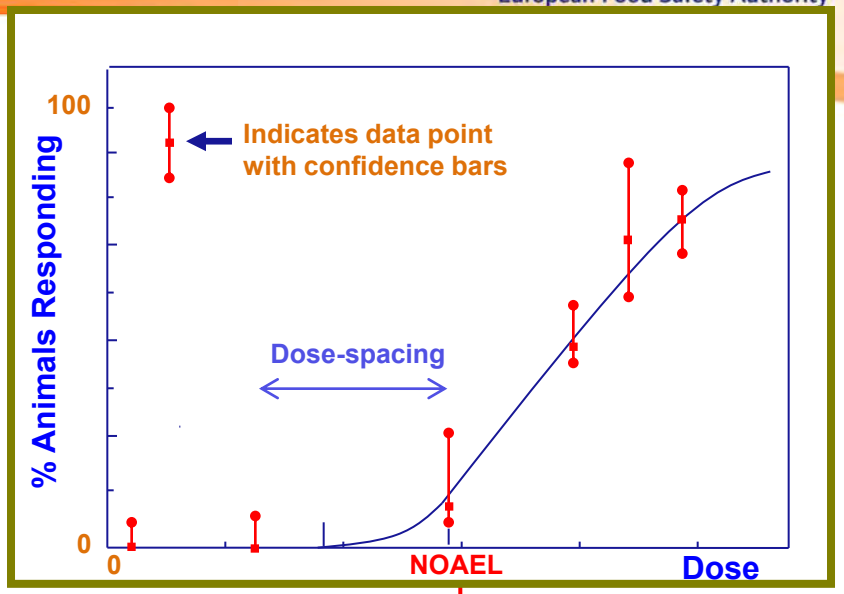
- Most sensitive species
- Lowest NOAEL
- Apply uncertainty factors (UF)



Establishing a Health Based Guidance Value

NOAEL (mg/kg bw) : UF = ADI / ARfD
TDI (mg/kg bw)
PTWI

animals

man

ADI: intentionally added compounds **TDI, PTWI: Contaminants**

Problematic Areas:

- **Allergies and intolerances**
- **Non-monotonic dose-response curves (D-R) e.g. vitamins, trace elements**
- **Assumption of a non-thresholded D-R e.g. genotoxic and carcinogenic compounds**

NOTE:
the existence of a threshold cannot be proven or disproven experimentally

The most difficult issue in food safety is to advise on potential risks to human health for unavoidable compounds found in food, which are both genotoxic and carcinogenic

- As low as reasonably achievable (ALARA)
- Dose-response extrapolation outside the observed dose range




Limitation of the ALARA approach

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ALARA = As Low As Reasonably Achievable

- Advice does not take into account available scientific information on potency of the compound and extent of human exposure
- Continuous improvement of analytical methods leads to lower detection limits and increases the number of genotoxic carcinogens detected in food
- ALARA does not provide risk managers with a scientific basis for setting priorities or for taking actions

Genotoxic and Carcinogenic Compounds

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Assumptions:

No Dose Without Effect ?

linear Dose-Response-Relationship?
(Line through Origin)

The Delaney amendment (the USA 1959) … no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal…

Stöhrer Arch Toxicol (1991)

Low-dose experiments ?

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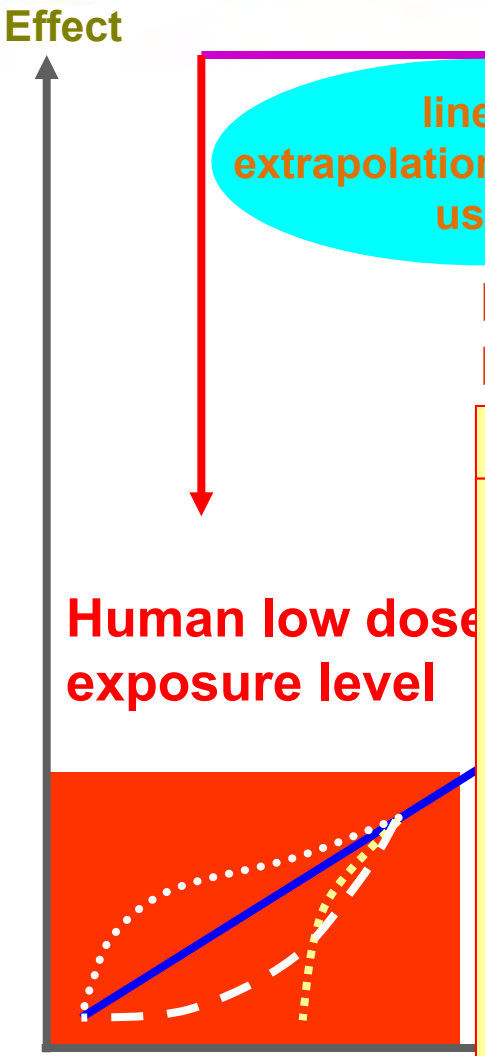

Group size for 5% wrong negative results (p<0.05)			
	number of animals per Group spontaneous tumour rate		
increase	1%	10%	20%
25%	40	65	82
20%	52	92	121
15%	74	147	202
10%	121	289	423
5%	295	979	1,546
0.1%	226,742	1,958,629	3,471,874

Extrapolation from observed range to Low-Dose Exposure ?

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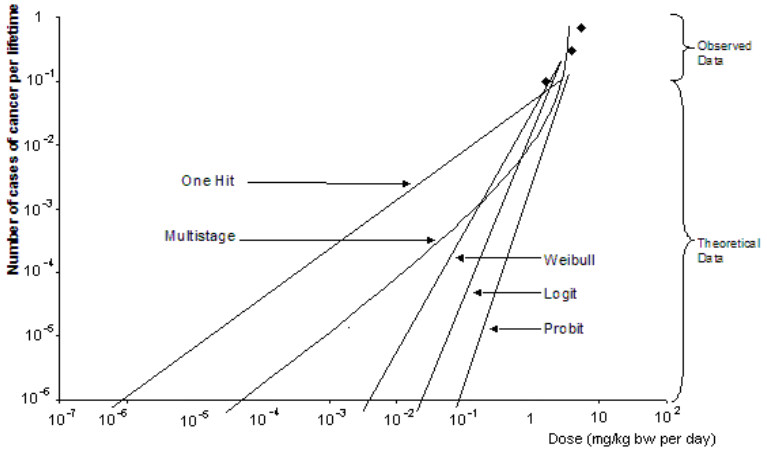
EFSA 2005:

has serious reservations about extrapolating outside the observed dose range using mathematical modelling

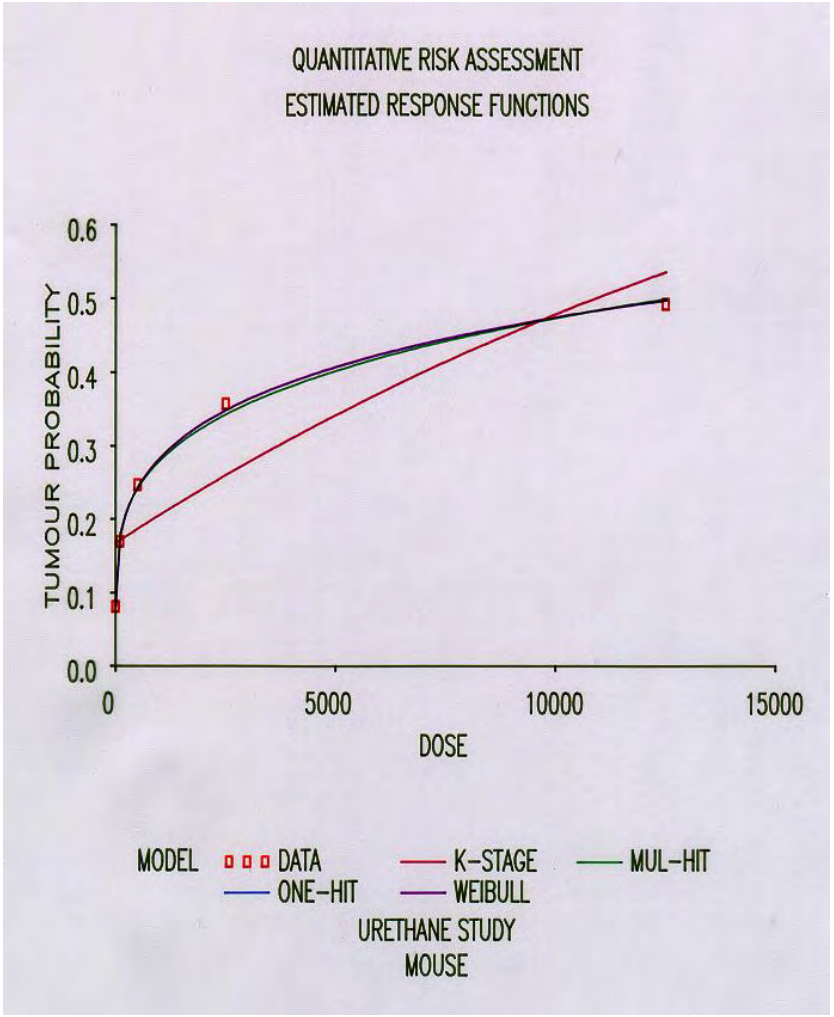


„Model used more important than actual data“

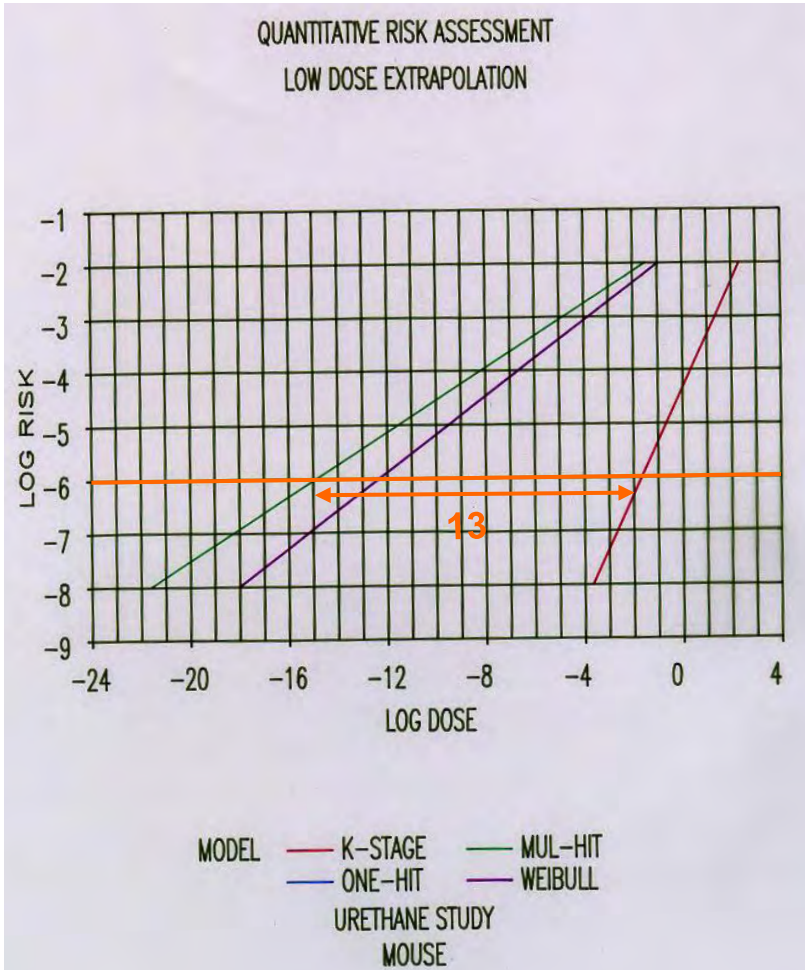
- sign. non-linearities in toxicokinetics and mode of actions
- cytotoxicity at high doses may influence the D-R

EFSA 2005: Opinion of the Scientific Committee on a request from EFSA related to A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic
http://www.efsa.europa.eu/en/efsajournal/doc/282.pdf

Example Ethyl Carbamate



Data from Schmähl *et al.* 1977



Modelling by Dr. Felix Wächter, Ciba Geigy Basel (1986)

Extrapolation from Observable Range to Low-Dose Exposure ?

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- Homeostatic and cytoprotective mechanisms
- Abundance of cellular targets

⇒ minimum degree of interaction of the substance with the critical sites must be reached to elicit a toxicologically relevant effect

- EFSA Scientific Committee is of the opinion that there is a 'practical' threshold for genotoxic compounds
- Levels below which cancer incidence is not increased cannot be identified on scientific grounds
- Margin of exposure approach (MOE) was considered appropriate for genotoxic compounds

MOE Definition: EHC 240

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Margin of exposure (MOE)

Ratio of the no-observed-adverse-effect level or benchmark dose lower confidence limit for the critical effect to the theoretical, predicted or estimated exposure dose or concentration.

Margin of safety

The margin between the *health-based guidance value* (reference dose) and the actual or estimated exposure dose or concentration.

MOE: Comparison of Reference Points

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Margin of Exposure (M O E):

Comparison of
Reference Dose from Animal Experiments
with
Human Exposure-dose

$$\text{MOE} = \frac{\text{dose producing tumours in animals}}{\text{human exposure dose}}$$

Reference Dose for Human Exposure

- **Human Exposure Assessment *is not different* to that for substances with another type of toxicological profile.**

- **Main concern is chronic exposure (EFSA):**

Dietary Intake estimates may relate to:

- ✓ **the whole population or preferably for "consumers only",**
- ✓ **the mean and median intakes,**
- ✓ **the intake by individuals highly exposed**
  (due to high consumption of some foods or to average consumption of highly contaminated foods), as represented by the 90th, 95th, 97.5th and 99th percentiles of the population group.

Reference Dose from Animal Experiments

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Proposal for a procedure:

European Food Safety Authority (EFSA)
http://www.efsa.europa.eu/en/efsajournal/doc/1150.pdf
International Programme on Chemical Safety (IPCS)
EHC 239: http://www.inchem.org/documents/ehc/ehc/ehc239.pdf

Modelling of the Dose-Response-Curve in the observable range by using mathematical and statistical Methods

Dose, causing a defined Incidence (=BMR) (often 10%) = B M D_{10}
BMDL: Lower Confidence Interval (95%)

64. JECFA (FAS 55, 2006): MOE approach for acrylamide, ethyl carbamate, and PAHs.
72. JECFA (FAS 63, 2011): MOE approach for acrylamide, furan, arsenic
http://www.who.int/foodsafety/chem/jecfa/publications/monographs/en/index.html

Optimising hazard characterisation

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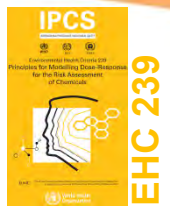
Dose-response analysis : moving from NOAEL to Benchmark Dose approach (EFSA 2009)



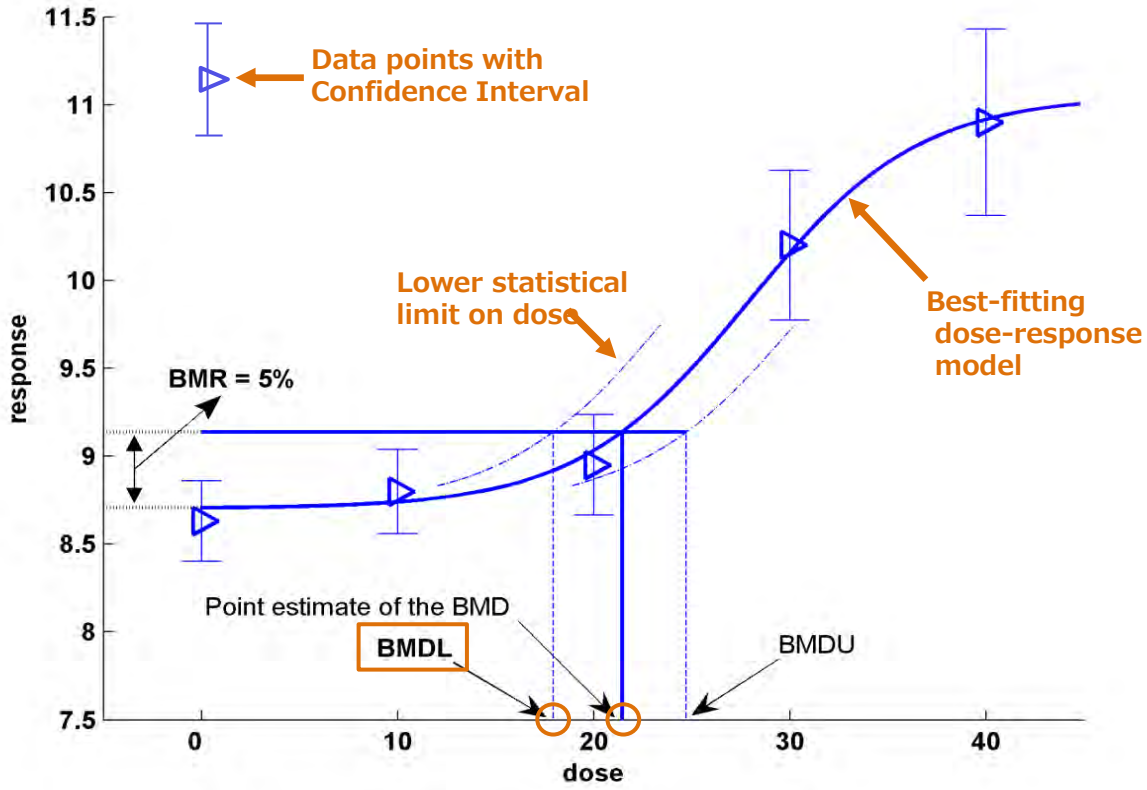
- The BMD approach offers a more scientific way of defining a reference point on the dose-response curve that can be used as the point of departure for risk characterisation
  - ✓ Use of the whole does-response data and no NOAEL is needed
  - ✓ Not dependent on dose-spacing
  - ✓ Evaluates the uncertainty in the calculated BMD

e.g.

- ❖ **Derivation of health-based guidance values for substances with thresholded effects**
- ❖ **Calculating margins of exposure for substances with non-thresholded effects – i.e. genotoxic & carc. compounds**

Guidance of the Scientific Committee on Use of the benchmark dose approach in risk assessment
http://www.efsa.europa.eu/en/efsajournal/doc/1150.pdf

The Benchmark Dose (BMD)



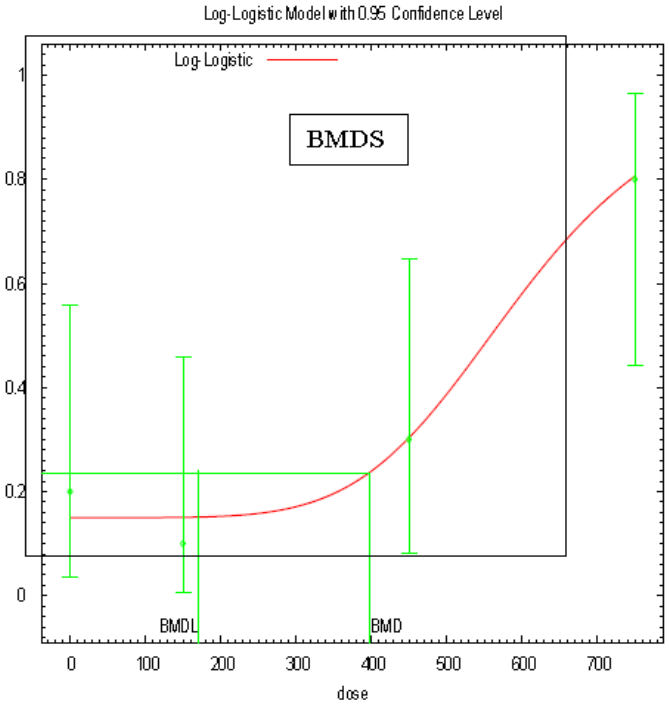
- Data from different Species
- Different Endpoints (organ-specific Tumour incidence, Total Tumours)
- Different Models

➢ Use lowest BMD(L) as reference point? Central estimate?

BMD- software

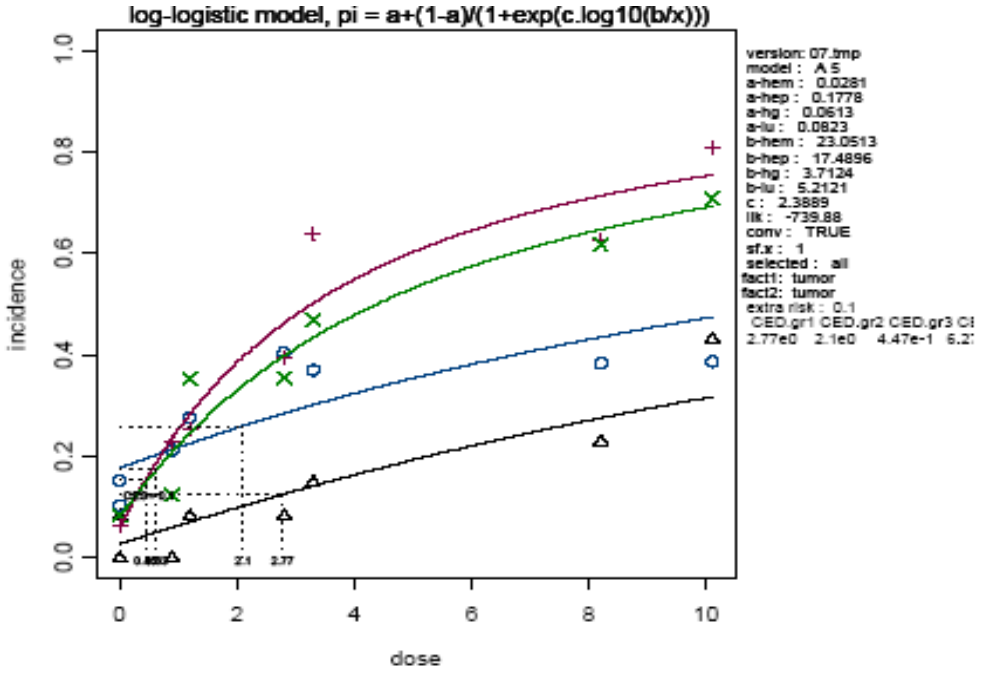
U.S. EPA BMDS:

http://www.epa.gov/ncea/bmds/index.html



PROAST :

http://www.rivm.nl/en/Library/Scientific/Models/PROAST



The MOE approach

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Moving from ALARA To MOE

$$\text{MOE} = \frac{\text{dose producing tumours in animals}}{\text{human exposure dose}}$$

- to provide additional scientific advice to risk managers taking into account available scientific information
  - Potency of compound
  - Extent of human exposure (average, high consumers)
- Selection of a reference point (point of departure): $BMDL_{10}$

- ✓ Magnitude of a MOE can be used for priority setting: a small MOE represents a higher risk than a larger MOE
- ✓ Magnitude of MOE which is acceptable is a societal judgment and is the responsibility of risk managers
- ✓ MOE makes no implicit assumptions on a "safe" intake

64. JECFA 2005, EFSA 2005

The MOE approach: interpretation

The EFSA Scientific Committee proposed in 2005 that, in general, an *MOE of 10'000 or higher*, if it is based on the *$BMDL_{10}$* from an animal study, would be *of low concern* from a public health point of view and might be considered as *a low priority for risk management actions*.

Based on considerations of:

- **inter-species differences (differences between animals and humans),**
- **intra-species differences (differences between human individuals),**
- **the nature of the carcinogenic process,**
- **the reference point on the dose-response curve.**

Example Ethyl Carbamate

- **Previously: industrial uses, veterinary/medical uses**
- **Today: Major route of exposure as fermentation by-product in food and beverages (stone fruit brandies)**
- **First identified as rodent carcinogen in 1940s: multisite carcinogen by any route in rodents**

Ethyl Carbamate: tumor data

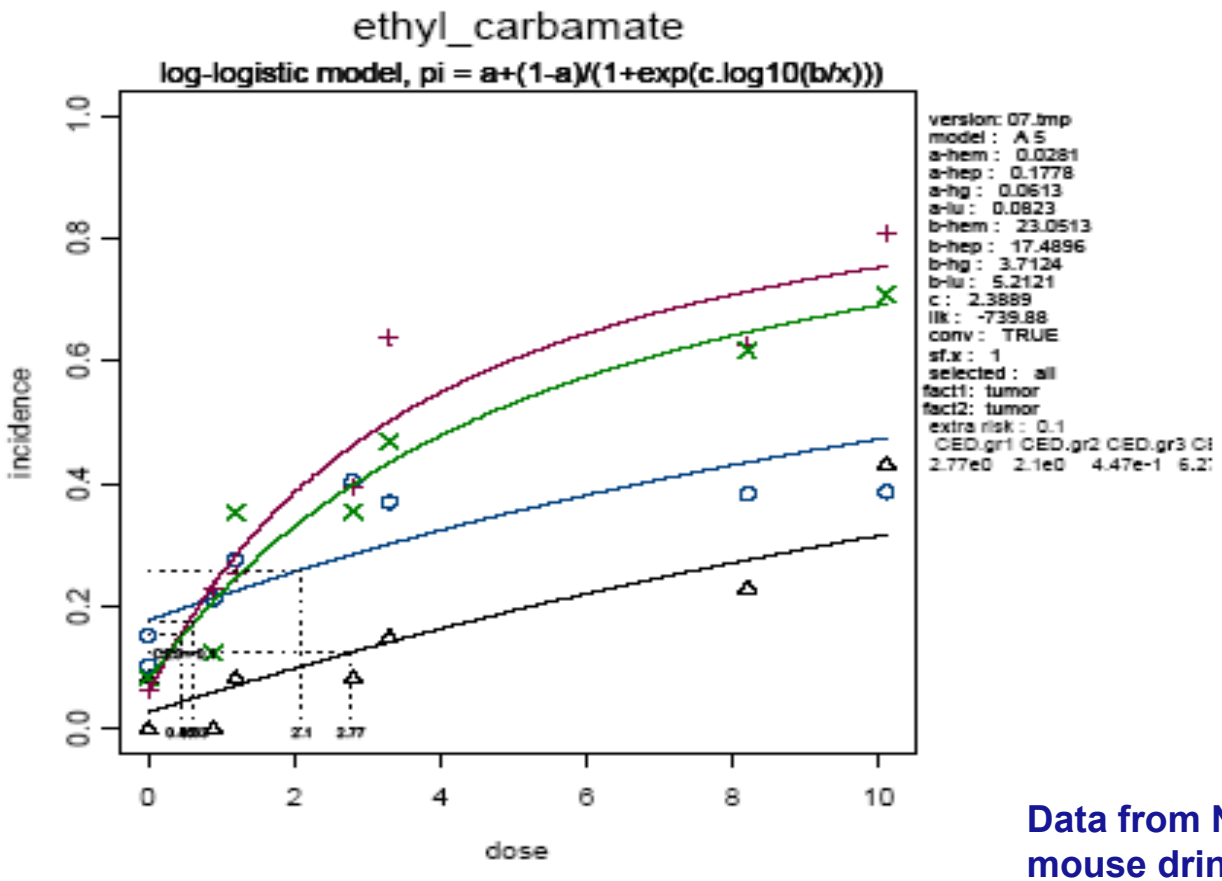
Table 3. Tumour incidences at selected organ sites from a 2-year carcinogenicity study in B6C3F1 mice administered ethyl carbamate at 0, 10, 30 or 90 mg/l in drinking-water containing 0%, 2.5% or 5% ethanol

	Ethyl carbamate concentration in drinking-water (mg/l)							
	Male B6C3F1 mice				Female B6C3F1 mice			
	0	10	30	90	0	10	30	90
Equivalent to ethyl carbamate dose (mg/kg bw per day) calculated from mean water consumption and mean body weight over mean life span (and mean weeks 1–13)								
0% ethanol	0	1.2 (1.5)	3.3 (4.7)	10.1 (13.1)	0	0.9 (1.4)	2.8 (4.3)	8.2 (12.9)
Lung, alveolar/bronchiolar adenoma or carcinoma								
0% ethanol[c]	5/48	18/48**	29/47**	37/48**	6/48	8/48	28/48**	39/47**

(NTP 2004, Beland et al. 2005)

Ethyl Carbamate: BMD modelling

Figure 3. Incidences of four tumour types. Plusses: Harderian glands (hg), crosses: lung (lu), circles: hepatocellular (hep), triangles: haemangiosarcoma (hem). Dose is in mg/kg bw per day.



Data from NTP 2004:
mouse drinking water
PROAST software

Ethyl Carbamate: 64 JECFA

Table 6. Ranges of BMD and BMDL values for tumours associated with administration of ethyl carbamate

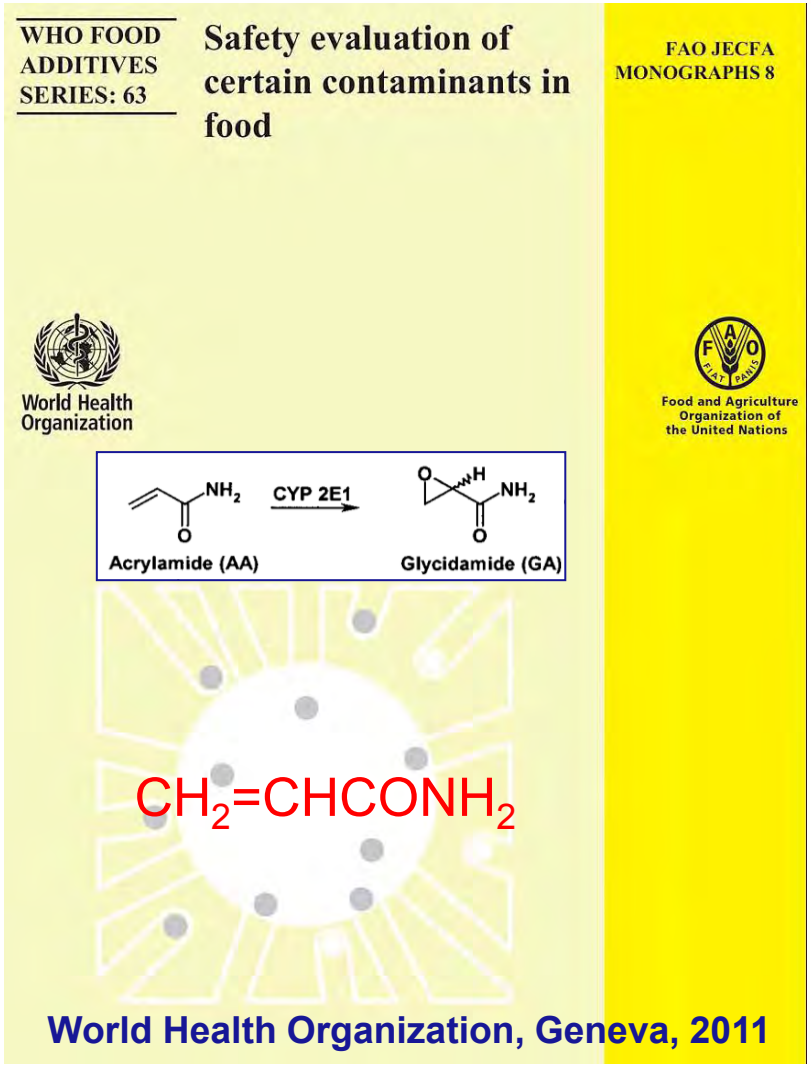
Tumour type	Range of BMD values (mg/kg bw per day)	Range of BMDL values (mg/kg bw per day)
Lung adenoma or carcinoma	0.50–0.63	0.26–0.51
Harderian gland adenoma or carcinoma	0.47–0.76	0.28–0.61

BMD, benchmark dose for 10% extra risk of tumors; BMDL, 95% lower confidence limit for the benchmark dose. Extra risk is defined as the additional incidence divided by the tumor-free fraction of the population in the controls.

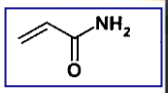
Ethyl Carbamate (Urethan)		**MOE**
BMDL	**0.3 mg/kg**	
Intake	**15 ng/kg**	**20´000**
	80 ng/kg (+ alcoholic Beverages)	**3´800**

Acrylamide


WHO FOOD ADDITIVES SERIES 55
Safety evaluation of certain contaminants in food
FAO FOOD AND NUTRITION PAPER
82
WORLD HEALTH ORGANIZATION
FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS
CYP 2E1
Acrylamide (AA)
Glycidamide (GA)
$CH_2=CHCONH_2$
IPCS
International Programme on Chemical Safety
World Health Organization – Geneva
2006


WHO FOOD ADDITIVES SERIES: 63
Safety evaluation of certain contaminants in food
FAO JECFA MONOGRAPHS 8
World Health Organization
Food and Agriculture Organization of the United Nations
CYP 2E1
Acrylamide (AA)
Glycidamide (GA)
$CH_2=CHCONH_2$
World Health Organization, Geneva, 2011

Example Acrylamide



Evaluated by JECFA in 2006 (FAS 55, 2006)
1st time ever the MOE approach was used

- ✓ is soluble in water and is evenly distributed in the body
- ✓ is **genotoxic**
- ✓ causes chromosome breaks in both *in vivo* and *in vitro*
- ✓ causes gene mutation in *in vivo* and *in vitro* systems (somatic and germinal cells)
- ✓ increases the **cancer incidence** in animals at 1-2 mg/kg bw
- ✓ IARC class 2A ("probably a human carcinogen")
- ✓ **is neurotoxic at "high" doses (NOEL 0.2 mg/kg bw for morphological changes in nerves)**

Tumor data

European Food Safety Authority

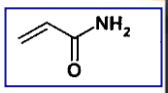


Table 3. Numbers of Fischer 344 rats with tumours at various organ sites after receiving drinking-water containing acrylamide for 2 years

Type of tumour	Sex	Dose[a] (mg/kg bw per day)				
		0	0.01	0.1	0.5	2.0
Thyroid gland, follicular adenomas	M	1/60	0/58	2/59	1/59	7/59*
Peritesticular mesotheliomas	M	3/60	0/60	7/60	11/60*	10/60*
Adrenal gland,[b] pheochromocytomas	M	3/60	7/59	7/60	5/60	10/60*
Mammary tumours	F	10/60	11/60	9/60	19/58	23/61*
Central nervous system, glial tumours	F	1/60	2/59	1/60	1/60	9/61*
Thyroid gland, follicular adenomas or adenocarcinomas	F	1/58	0/59	1/59	1/58	5/60*
Oral cavity, squamous papillomas	F	0/60	3/60	2/60	1/60	7/61*
Uterus, adenocarcinomas	F	1/60	2/60	1/60	0/59	5/60*
Clitoral gland, adenomas[c]	F	0/2	1/3	3/4	2/4	5/5*
Pituitary adenomas[b]	F	25/59	30/60	32/60	27/60	32/60*

Data from Johnson et al. (1986), as compiled by Rice (2005)

FAS 55, 2006

Tumor data

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Table 4. Numbers of Fischer 344 rats with tumours at various organ sites after receiving drinking-water containing acrylamide for 2 years[a]

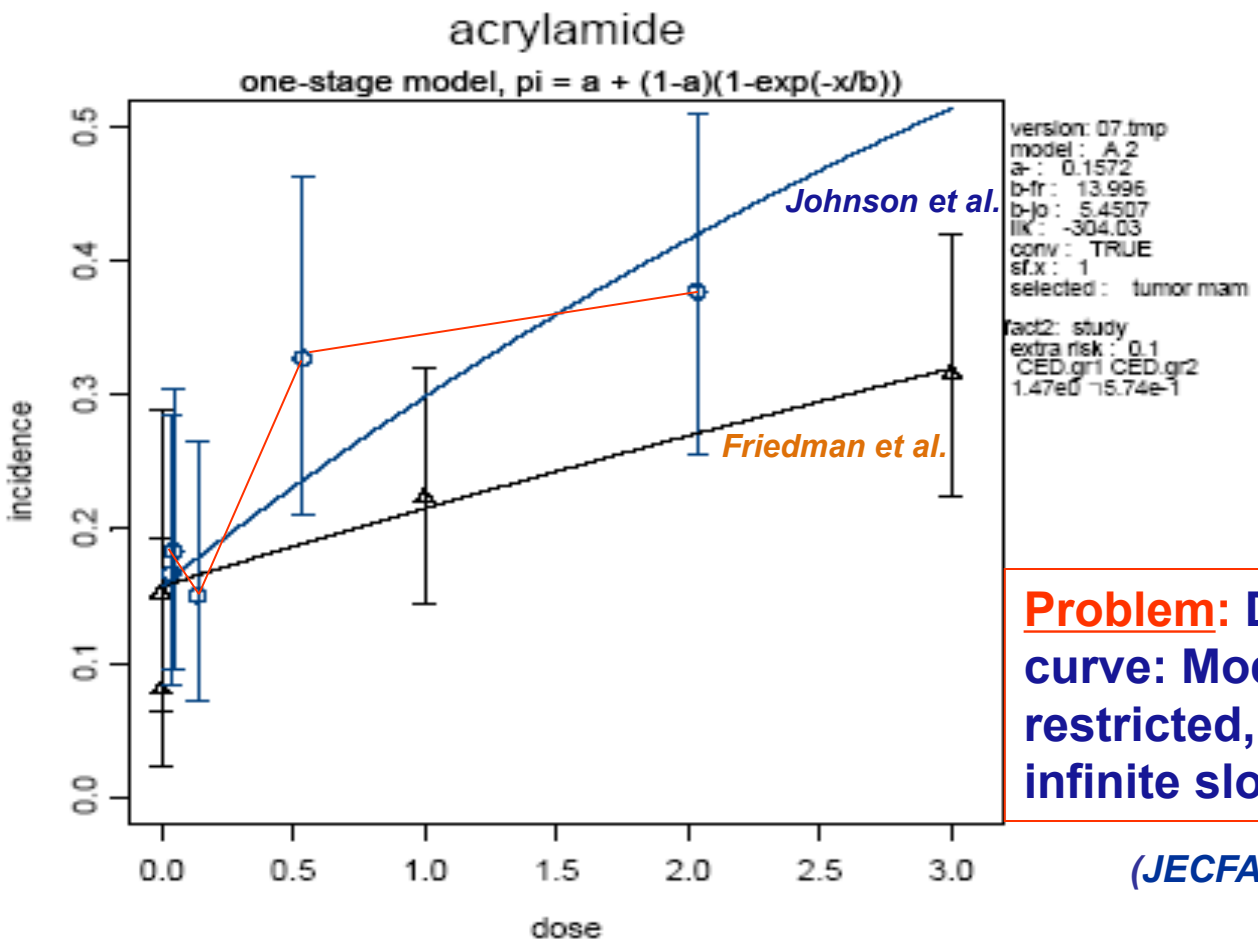
Type of tumour	Sex	Dose[b] (mg/kg bw per day)						
		0	0	0.1	0.5	1.0	2.0	3.0
Peritesticular mesotheliomas	M	4/102	4/102	9/204	8/102	–	13/75*	–
Brain and spinal cord, glial neoplasms[c]	M	1/102[d]	1/102[d]	2/204[e]	1.102[f]	–	3/75[d]	–
	F	0/50[g]	0/50[g]	–	–	2/100[g]	–	2/100[g]
Thyroid gland, follicular adenomas	M	2/100	1/102	9/203	5/101	–	15/75*[h]	–
	F	0/50	0/50	–	–	7/100	–	16/100*[h]
Thyroid gland, follicular cell carcinomas	M	1/100	2/102	3/203	0/101	–	3/75	–
	F	1/50	1/50	–	–	3/100	–	7/100
All follicular cell neoplasms	M	3/100	3/100	12/203	5/101	–	17/75	–
	F	1/50	1/50	–	–	10/100	–	23/100*
Mammary gland, fibroadenomas and adenocarcinomas	F	7/46	4/50	–	–	21/94*	–	30/95*

Data from Friedman et al. (1995), as compiled by Rice (2005)

FAS 55, 2006

BMD modelling mammary tumours

Figure 8. Incidences of total mammary tumours, with fitted one-stage model. Circles: Johnson et al. (1986); triangles: Friedman et al. (1995). Dose is expressed in mg/kg bw per day.



Problem: Dose-response-curve: Model needs to be restricted, otherwise infinite slope at 0 !!

(JECFA 64, FAS 55, 2006)

BMD Modelling

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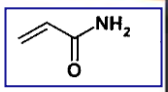
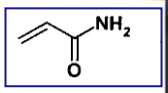


Table 17. Summary of the results of dose–response modelling for induction of selected tumours in rats given drinking-water containing acrylamide

Tumour	Study			
	Johnson et al. (1986)		Friedman et al. (1985)	
	Range of BMD (mg/kg bw per day)	Range of BMDL (mg/kg bw per day)	Range of BMD (mg/kg bw per day)	Range of BMDL (mg/kg bw per day)
Total mammary tumours	0.48–0.57	0.30–0.46	1.4–1.5	0.89–1.1
Peritesticular mesothelioma	0.97	0.63–0.97	NA	NA
Thyroid follicular adenoma	NA	NA	0.88–1.2	0.63–0.93
Central nervous system tumours of glial origin	1.9–2.0	1.3–1.6	NA	NA

BMD, benchmark dose for 10% extra risk of tumours; BMDL, 95% lower confidence limit for the benchmark dose. Extra risk is defined as the additional incidence divided by the tumour-free fraction of the population in the controls; NA, not applicable ***(JECFA 64, FAS 55, 2006)***

Intake estimates: Summary

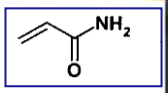


- Average national intake 0.3 - 2.0 µg/kg bw per day
- 90. - 97.5 percentile: 0.6 - 3.5 µg/kg bw per day
- 99. Percentile: up to 5.1 µg/kg bw per day
- Children: about 2–3x higher than adults on bw basis

- international average intake: 3.0–4.3 µg/kg bw per day (GEMS/Food regional diets, bw 60 kg).

JECFA: concluded that based on national estimates, an intake of acrylamide of **1 µg/kg bw per day** could be taken to represent the average for the general population and that an intake of **4 µg/kg bw per day** could be taken to represent consumers with a high intake. Children are also included in these estimates for average to high intake.

Conclusion JECFA 64



Avergage intake: 1 ug/kg bw
High consumer: 4 ug/kg bw

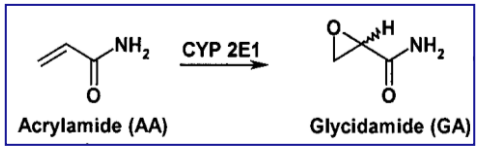
NOAEL neurotoxicity : 200 ug/kg bw
Lowest BMDL10: 300 ug/kg bw

	MOE (1 ug/kg bw)	MOE (4 ug/kg bw)
neurotoxicity	200	50
carcinogenicity	300	75

The Committee considered these MOEs to be low for a compound that is genotoxic and carcinogenic and that this may indicate a health concern

72nd JECFA 2010 (FAS 63, 2011)

New carcinogenicity studies (Beland 2010)



equimolar concentrations of acrylamide (and glycidamide) in the drinking water of B6C3F1 mice and Fisher 344 rats:

Drinking water concentration :	0.0875	0.175	0.35	0.7	mmol/l
AA dose male mice:	1.05	2.23	4.16	9.1	mg/kg bw
AA dose female mice:	1.11	2.25	4.71	9.97	mg/kg bw
AA dose male rats:	0.34	0.67	1.36	2.78	mg/kg bw
AA dose female rats:	0.45	0.9	1.88	4.09	mg/kg bw

Carcinogenicity study: mice

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Table 6. Incidence of neoplasms in acrylamide-treated male and female B6C3F1 mice

Sex	Neoplastic or non-neoplastic finding	Poly-3 survival-adjusted incidence (%)				
		0 mmol/l[a]	0.0875 mmol/l[a]	0.175 mmol/l[a]	0.35 mmol/l[a]	0.70 mmol/l[a]
Male	Harderian gland adenoma	4.8*	29.1**	59.7**	78.8**	87.5**
	Harderian gland adenoma or carcinoma	4.8*	29.1**	59.7**	81.0**	87.5**
	Lung alveolar/bronchiolar adenoma	11.9*	13.8	29.8**	23.5	47.0**
	Lung alveolar/bronchiolar adenoma or carcinoma	14.3*	13.8	32.1**	23.5	49.5**
	Forestomach squamous cell papilloma	0.0*	4.5	4.6	13.5	15.3**
Female	Forestomach squamous cell papilloma or carcinoma	0.0*	4.5	4.6	15.7**	20.4**
	Harderian gland adenoma	0.0*	17.8**	44.7**	73.5**	74.9**
	Lung alveolar/bronchiolar adenoma	2.2*	8.9	13.7	29.2**	52.1**
	Lung alveolar/bronchiolar adenoma or carcinoma	4.5*	8.9	13.7	29.2**	54.8**
	Mammary gland adenocarcinoma	0.0*	8.9	13.8**	5.2	33.4**
	Mammary gland adenoacanthoma	0.0*	2.3	2.3	5.3	10.8**
	Mammary gland adenocarcinoma or adenoacanthoma	0.0*	8.9	13.8**	5.2	35.4**
	Ovarian benign granulosa cell tumour	0.0*	2.4	0.0	2.7	15.2**

* Significant ($P < 0.05$) trend; ** significantly different ($P < 0.05$) from the control group (0 mmol/l).

[a] Equivalent to 0, 1.05, 2.23, 4.16 and 9.11 mg/kg bw per day in males and 0, 1.11, 2.25, 4.71 and 9.97 mg/kg bw per day in females.

Carcinogenicity study: rats

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Table 9. Incidence of neoplasms in glycidamide-treated male and female F344 rats

Sex	Neoplastic or non-neoplastic finding	Poly-3 survival-adjusted incidence (%)				
		0 mmol/l[a]	0.0875 mmol/l[a]	0.175 mmol/l[a]	0.35 mmol/l[a]	0.70 mmol/l[a]
Male	Testicular mesothelioma	0.0*	2.8	11.0	28.1**	51.2**
	Heart malignant schwannoma	5.3*	8.2	8.3	17.1	26.3**
	Oral cavity papilloma squamous or papilloma	2.6*	5.4	0.0	5.9	23.7**
	Oral cavity squamous cell carcinoma, papilloma squamous or papilloma	5.3*	5.4	2.7	5.9	23.7**
	Thyroid gland follicular cell adenoma	5.4*	3.0	8.1	8.9	31.3**
	Thyroid gland follicular cell carcinoma	0.0*	5.8	8.2	2.9	18.2**
	Thyroid gland follicular cell adenoma or carcinoma	5.4*	8.8	16.0	11.6	46.2**
	Mononuclear cell leukaemia	49.4*	60.2	65.4	65.2	76.0**
Female	Clitoral gland carcinoma	9.3*	14.5	17.0	29.8**	45.1**
	Clitoral gland adenoma or carcinoma	20.8*	19.3	29.1	35.1	52.2**
	Mammary gland fibroadenoma	35.9*	59.3	81.3	85.1	90.5**
	Mammary gland fibroadenoma or adenocarcinoma	37.7*	59.3	82.6	86.3	91.6**
	Oral cavity squamous cell carcinoma, papilloma squamous or papilloma	2.3*	4.9	5.0	5.5	24.7**
	Thyroid gland follicular cell adenoma	0.0*	7.3	7.6	5.7	19.1**
	Thyroid gland follicular cell adenoma or carcinoma	0.0*	7.3	12.4	11.4	29.5**
	Mononuclear cell leukaemia	26.2*	23.1	47.3	47.7	69.6**

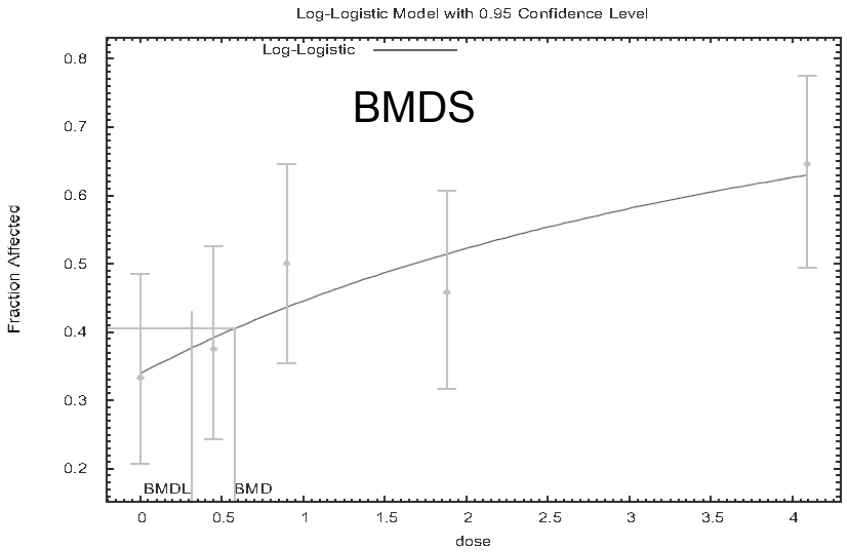
* Significant ($P < 0.05$) trend; ** significantly different ($P < 0.05$) from the control group (0 mmol/l).

[a] Equivalent to 0, 0.39, 0.80, 1.59 and 3.40 mg/kg bw per day in males and 0, 0.55, 1.10, 2.27 and 4.72 mg/kg bw per day in females.

BMD modelling: mice

Table 21. Individual model results for male mouse Harderian gland adenoma or carcinoma

Model name	*P*-value	BMD_{10}[a]	$BMDL_{10}$[a]
Gamma	0.024	*0.41*	*0.34*
Logistic	0.000	*1.00*	*0.84*
Log-logistic	0.257	0.37	0.18
Log-probit	0.049	0.66	0.55
Multistage	0.024	*0.41*	*0.34*
Multistage cancer	0.024	*0.41*	*0.34*
Probit	0.000	*1.03*	*0.89*
Weibull	0.024	*0.41*	*0.34*
Quantal linear	0.024	*0.41*	*0.34*

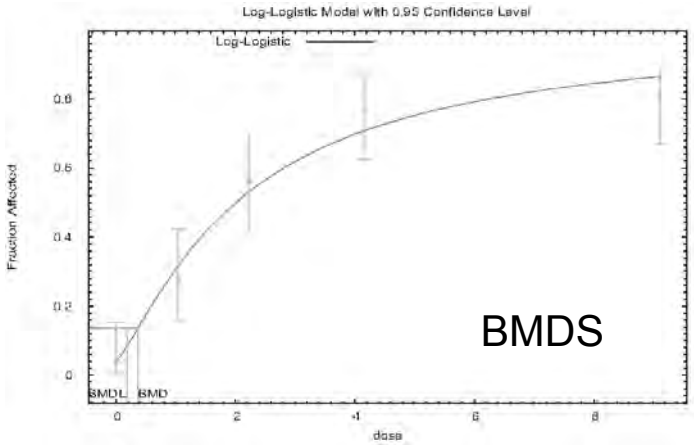


[a] BMD values in italics were excluded on the basis of fit.

BMD modelling: rats

Table 22. Individual model results for female rat mammary gland fibroadenoma

Model name	*P*-value	BMD_{10}	$BMDL_{10}$
Gamma	0.68	0.73	0.46
Logistic	0.66	0.94	0.67
Log-logistic	0.68	0.58	0.31
Log-probit	0.52	1.35	0.87
Multistage	0.68	0.73	0.46
Multistage cancer	0.68	0.73	0.46
Probit	0.66	0.93	0.67
Weibull	0.68	0.73	0.46
Quantal linear	0.68	0.73	0.46



BMDS

Conclusion JECFA 72

Exposure to AA had not changed:
Avergage intake: 1 ug/kg bw
High consumer: 4 ug/kg bw
NOAEL neurotoxicity : 200 ug/kg bw

Lowest BMDL10: **180 ug/kg bw (Harderian gland mice)**
310 ug/kg bw (Mammary gland rat)

	MOE (1 ug/kg bw)	MOE (4 ug/kg bw)
Harderian gland mice	180	45
Mammary gland rat	310	78

The Committee considered that for a compound that is both genotoxic and carcinogenic, these MOEs indicate a human health concern.

Discussion

Advantages of MOE

- Pragmatic approach
- Uses both intake and potency
- Does not extrapolate outside range of observations
- Estimates uncertainties that can inform future needs
- Can be used to prioritize risk management actions
- Can be used to compare and rank compounds
- Does not generate a numerical upper bound risk estimate that is open to misinterpretation

Discussions

Disadvantages of MOE

- The numerical value gives no indication of the actual risk although the higher the MOE the lower the risk
- Because the MOE is a ratio, good intake data are as important as good dose-response data
- Interpretation of the significance of a particular value lies on the borderline between risk assessment and risk management

Discussions

Application of the MOE approach within EFSA:

- **Mainly in the area of contaminants:**
  (Acrylamide, Aflatoxins, Ethyl carbamate, pyrrolizidine alkaloids, Polycyclic aromatic hydrocarbons)
  As, Mineral oil hydrocarbons, "non dioxin-like PCB", Brominated flame retardants (polybrominated diphenyl ethers, Brominated phenols, tetrabrom obisphenol A, hexabromocyclododecanes), Lead, Marine biotoxins (cyclic imines),

- **safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed**
  http://www.efsa.europa.eu/en/efsajournal/doc/2578.pdf
  http://www.efsa.europa.eu/en/efsajournal/pub/2578.htm

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http://www.efsa.europa.eu/en/efsajournal/doc/282.pdf

Thank you very much for your attention !