The use of dose response data for risk assessment

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Previous advice on substances in food that are genotoxic and carcinogenic

- Exposure should be reduced to As Low As Reasonably Achievable/Practicable (ALARA/P)
- not authorised for food use
  - not permitted as pesticides, veterinary medicines or food additives
- For natural constituents and unavoidable contaminants, need to consider what can realistically be achieved
- ALARA has been criticised as not informative as it does not take into account exposure or potency

Genotoxic substances in food

Process contaminants

acrylamide

heterocyclic amines, PAHs

ethylcarbamate

furan

chloropropanols

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Natural toxicants and contaminants

Methyleugenol

benzene

aflatoxins

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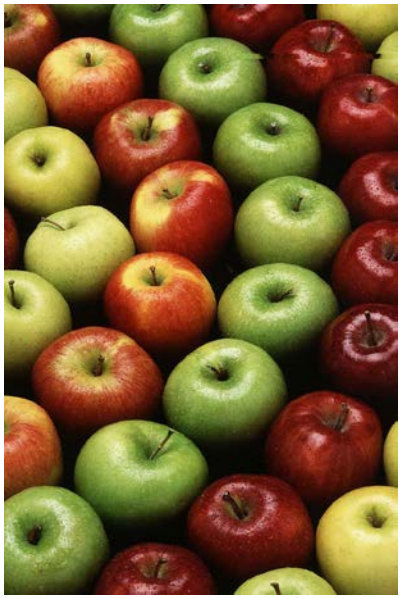
Adulterants and impurities

sudan dyes

leucomalachite green



1-Methylcyclopropene impurities

Development of the MOE approach

- Recent initiatives in risk assessment of compounds that are genotoxic and carcinogenic
  - 64th JECFA, Feb 2005
  - EFSA opinion, Oct 2005
  - ILSI Expert Group (O'Brien *et al*., 2006)
  - WHO/EFSA/ILSI conference, Nov 2005 (Barlow *et al*., 2006)
  - ILSI Expert Group (Benford *et al*., 2010)
  - ILSI Expert group (Edler *et al*., 2014)

MoE approach

- Margin of Exposure (MoE)
  - ratio of a defined point of departure (PoD) on dose response curve to estimated human intake
  - Preferred PoD is the lower confidence interval of the Bench Mark Dose resulting in 10% increased tumour incidence ($BMDL_{10}$)
  - larger the MoE the lower the concern
  - EFSA considered MOE of 10,000 is of “low concern” when based on $BMDL_{10}$ from animal bioassay

MOE of 10,000

- EFSA (2005)
  - 100 for uncertainties in inter- and intra-species differences
  - 100 for uncertainties in the carcinogenic process

- Equated to upper bound risk of 1 in 10^5 by some authorities

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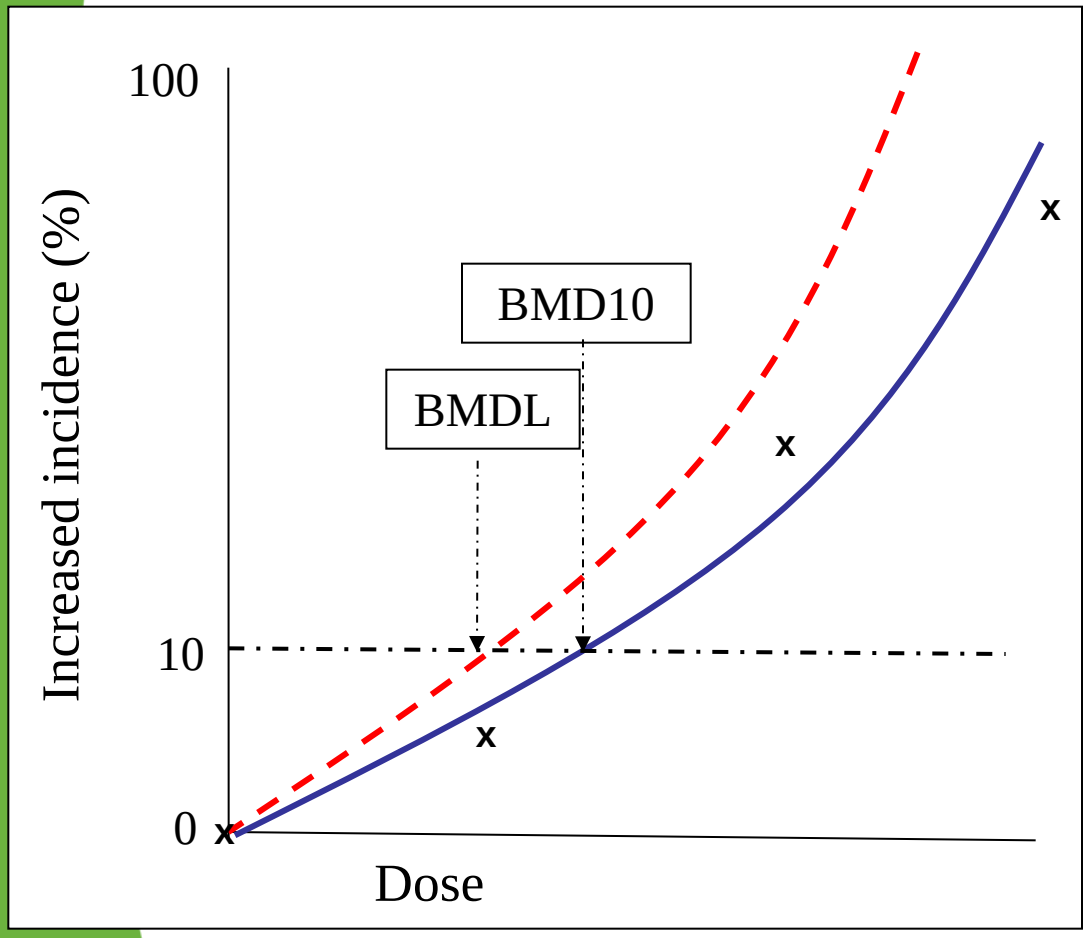
MoE - Dose-response

Benchmark dose approach preferred (WHO, 2004)



Uses all of the data

BMDL reflects quality of data

Can also extrapolate from point of departure to low doses

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Key issues - exposure

- Extensive data for some substances, reliance on scenarios for others
- Highly conservative if exposure is expected to be intermittent
  - E.g. infrequently consumed foods
- MOEs not comparable for intermittent vs continuous exposure
- Approach is determined by the questions from risk managers
- Issues generally not specific to substances that are genotoxic and carcinogenic

Key issues – Point of Departure

- Selection of tumour dataset
  - which endpoints (tumour types) are potentially relevant for humans?
  - Which is the critical endpoint when there are a number of tumour types?
  - Quality of cancer data for dose-response modelling
- Selection of models
    - To constrain or not to constrain
- Selection of BMDL

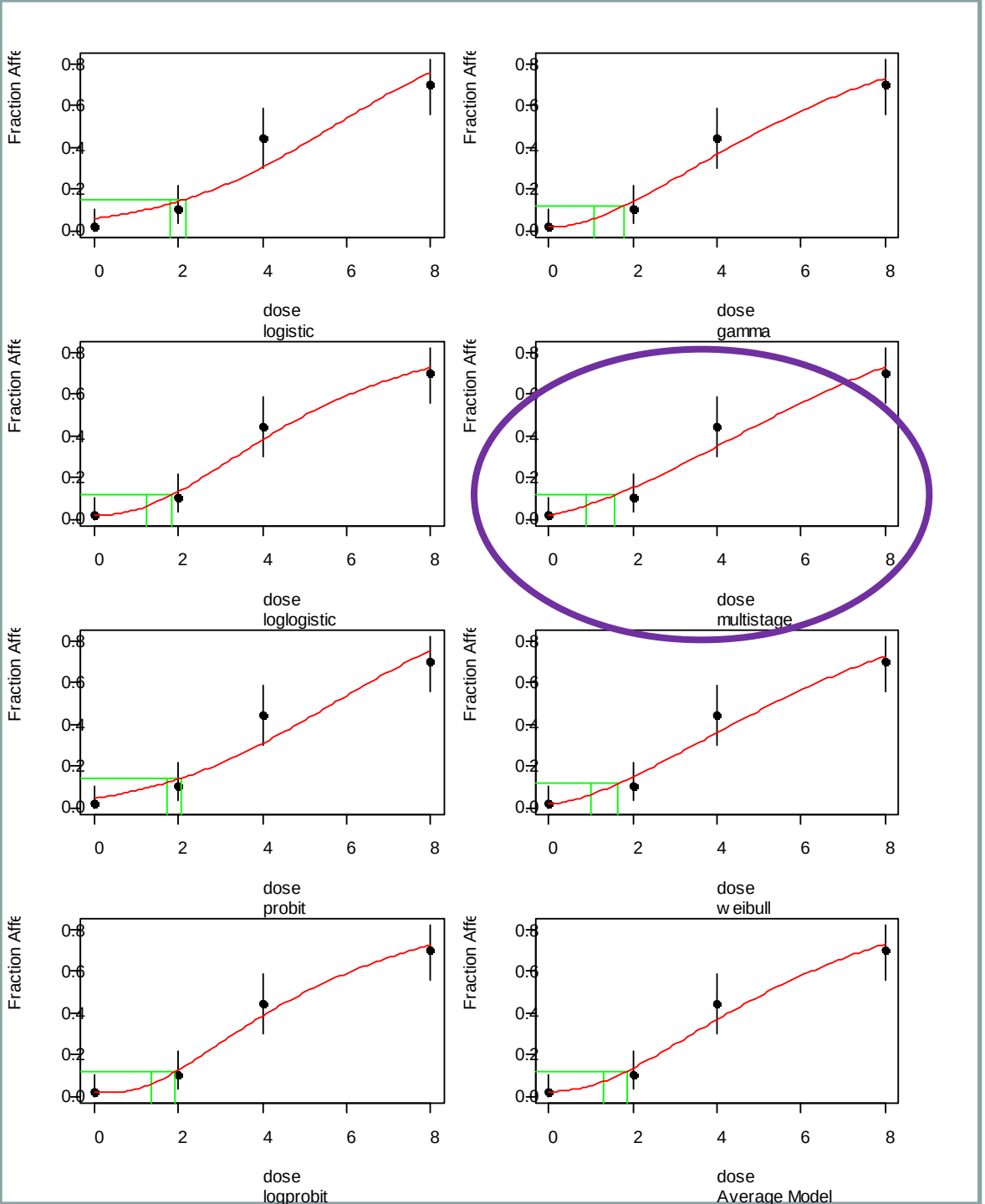
Dose-response modelling

- Tumours with significant dose-related trend and potentially relevant to humans
- Modelling (quantal)
  - BMDS software (http://www.epa.gov/NCEA/bmds/)
    - Suite of models
    - Select model with acceptable fit to the data and lowest BMDL
    - Model average approach (Wheeler and Bailer, 2007)
  - PROAST (http://www.rivm.nl/en/Documents_and_publications/Scientific/Models/PROAST)
    - Contains additional models

Furan – carcinogenicity data

Rat	Dose mg/kg/day, 5days/week, gavage			
	0	2	4	8
Male				
2-year survival	33/50	28/50	26/50	16/50
Cholangiocarcinoma	0/50	43/50	48/50	49/50
Hepatocellular adenoma or carcinoma	1/50	5/50	22/50	35/50
Mononuclear cell leukaemia	8/50	11/50	17/50	25/50
Female				
2-year survival	34/50	32/50	28/50	19/50
Cholangiocarcinoma	0/50	49/50	50/50	48/50
Hepatocellular adenoma or carcinoma	0/50	2/50	4/50	8/50
Mononuclear cell leukaemia	8/50	9/50	17/50	21/50

- Cholangiocarcinoma considered to have arisen by mechanism involving oxidative stress
- Hepatocellular adenoma/carcinoma selected as most relevant endpoint



Furan

Gavage study, dosing 5 days per week.

Hepatocellular adenoma/carcinoma in male rats

BMD_{10}: 1.57-2.19 mg/kg bw/d

$BMDL_{10}$: 0.87-1.80 mg/kg bw/d

Model average
BMD_{10}: 1.84 mg/kg bw/d
$BMDL_{10}$: 1.28 mg/kg bw/d

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The MOEs

- MOEs calculated for average exposure for illustrative purposes
  - exposure data were not comparable in this exercise
- Rounded to 1 significant figure in view of uncertainties
- MOEs ranged over c. 6 orders of magnitude based on average exposure estimates

MOEs (Benford *et al.*, 2010)

Substance	BMD_{10} (mg/kg bw/day)	$BMDL_{10}$ (mg/kg bw/day)	MOE
Acrylamide - mammary tumours	0.50	0.16	200
Acrylamide - peritesticular mesothelioma	1.50	1.00	1000
Aflatoxin B1	0.00039	0.00025	600
BaP in PAHs	0.17	0.12	20,000
Benzene	32	18	6,000,000
1,3-Dichloro-2-propanol	13	10	100,000
Ethyl carbamate	0.5	0.25	20,000
Furan	1.84	1.28	4000
Leucomalachite green	40	20	4,000,000
1MCP impurities	27	11	100,000,000
Methyl eugenol	16	8	800
PhIP - mammary tumours	1.3	0.74	100,000
PhIP - prostate tumours	0.79	0.48	80,000
Sudan I	13	7	30-2,000,000

Uncertainty

- Essential to have narrative closely associated with the MOE value, describing the uncertainties
  - Level of uncertainty is not comparable between the case studies
  - Cannot quantify overall uncertainty
  - Use of confidence intervals does not capture all uncertainty in the PoD
  - Exposure data were for illustrative purposes and not comparable

Proposed framework

- Points to consider in conducting an MOE assessment, under following headers:
  - Purpose of the assessment
  - Mode of action
  - Selection of tumour data
  - Dose response modelling
  - Selection of PoD
  - Exposure assessment
  - Presentation of the MOE
- Benford *et* al., Food & Chemical Toxicology, Vol 48 S1, January 2010

Data selection for BMD modelling

- Edler *et al*., 2014
- Human relevance of tumours
  - Possible mode of action
  - Species-specific effects
  - Anatomical sites not present in humans
- Statistical aspects
- Uncertainty analysis

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Why we need an analagous approach for genotoxicity data

- Need to provide risk assessment advice on substances for which it is not possible to calculate a $BMDL_{10}$ for carcinogenicity
  - High incidence of tumours at all doses
  - No carcinogenicity data for a genotoxic substance
  - Often needed in hours/days
- What about germ cell mutagens?

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Key issues – Point of Departure

- Selection of dataset
  - Which endpoint is most sensitive/relevant?
  - Species/cell type
  - In vivo study design – single/repeat dose?
  - Are data suitable for dose-response modelling?
  - Use of in vitro data with PBTK extrapolation to in vivo?
- Critical effect size (benchmark response)
- Selection of models
  - Datasets that do not give a good fit
- Selection of BMDL

How do we interpret the MOE?

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Conclusions

- The MOE approach for substances that are genotoxic and carcinogenic has developed over about 10 years, based on carcinogenic potency
- Depending on the approach taken it is possible to generate many different BMDL values for one substance. Therefore a systematic and transparent approach is required
- An analogous MOE approach based on genotoxic potency would provide a valuable tool for risk assessors and regulators
- Development of such an approach should take into account the lessons learnt from the MOE for carcinogenicity
- The big challenges are how to interpret the value of an MOE, and how to use germ cell mutagenicity in risk assessment.

Thank you

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