ANNEX 1

REPORTS AND OTHER DOCUMENTS RESULTING FROM PREVIOUS MEETINGS OF THE JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES


4. Specifications for identity and purity of food additives (food colours) (Fourth report of the Joint FAO/WHO Expert Committee on Food Additives). These specifications were subsequently revised and published as Specifications for identity and purity of food additives, Vol. II. Food colours, Rome, Food and Agriculture Organization of the United Nations, 1963 (out of print).


63. Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 18, 1983.

64. Specifications for the identity and purity of certain food additives. FAO Food and Nutrition Paper, No. 28, 1983.


71. **Specifications for the identity and purity of certain food additives**. FAO Food and Nutrition Paper, No. 34, 1986.


75. **Specifications for the identity and purity of certain food additives**. FAO Food and Nutrition Paper, No. 37, 1986.


121. Residues of some veterinary drugs in animals and foods. FAO Food and Nutrition Paper, No. 41/8, 1996.


ANNEX 2

ABBREVIATIONS USED IN THE MONOGRAPHS

3-APA 3-aminopropionamide
8-OH-dG 8-hydroxy-2'-deoxyguanosine
AA acrylamide
ABS acrylonitrile–butadiene–styrene
ADI acceptable daily intake
AED atomic emission detection
Ah aryl hydrocarbon
AhR aryl hydrocarbon receptor
ALARA as low as reasonably achievable
ALT alanine transferase
AR androgen receptor
ARA arachidonic acid
ARfD acute reference dose
ATDS Australian Total Diet Survey
AUC area under the curve
BCG Bacillus Calmette-Guérin
BDE brominated diphenyl ether
BMD benchmark dose
BMDL lower confidence limit on the benchmark dose
BMR benchmark response
Br-GC-MS bromination–gas chromatography–mass spectrometry
BROD benzylxoyresorufin O-deethylase
bw body weight
CAS Chemical Abstracts Service
CCFAC Codex Committee on Food Additives and Contaminants
cGMP cyclic guanosine monophosphate
CI confidence interval
CIAA Confederation of Food and Drink Industries of the European Union
COX prostaglandin H synthase
CRM certified reference material
CV coefficient of variation
CYP cytochrome P450
Cys cysteine
da deoxyadenosine
dC deoxyctydine
DDT dichlorodiphenyltrichloroethane
dG deoxyguanosine
DHT dihydrotesterone
DNA deoxyribonucleic acid
EA early antigen

- 755 -
EC₅₀  median effective concentration
ECD  electron capture detection
ECNI  electron capture negative ionization
ED₅₀  median effective dose
E1  electron impact
ELISA  enzyme-linked immunosorbent assay
EPA  Environmental Protection Agency (USA)
ER  estrogen receptor
EROD  7-ethoxyresorufin O-deethylase
ESI  electrospray ionization
EU  European Union
FAO  Food and Agriculture Organization of the United Nations
FCA  Freund's complete adjuvant
FD  fluorescence detection
FID  flame ionization detection
FOB  functional observational (test) battery
FSH  follicle stimulating hormone
FT3  free triiodothyronine
FT4  free thyroxine
GA  glycidamide
GC  gas chromatography
GD  gestation day
GEMS/Food  Global Environment Monitoring System Food Contamination Monitoring and Assessment Programme
GM-CSF  granulocyte-macrophage colony stimulating factor
GSD  geometric standard deviation
GST  glutathione-S-transferase
GSTM1  glutathione-S-transferase M1
GSTT1  glutathione-S-transferase T1
hAR  human androgen receptor
HPLC  high-performance liquid chromatography
HRGC  high-resolution gas chromatography
HRMS  high-resolution mass spectrometry
IARC  International Agency for Research on Cancer
IC₅₀  median inhibitory concentration
IEF  induction equivalency factor
Ig  immunoglobulin
IGF  insulin-like growth factor
i.m.  intramuscular
i.p.  intraperitoneal
IPCS  International Programme on Chemical Safety
IRIS  Integrated Risk Information System
IU  international units
IUPAC  International Union for Pure and Applied Chemistry
JECA  Joint FAO/WHO Committee on Food Additives
JMPR  Joint FAO/WHO Meeting on Pesticide Residues
Kᵢ  inhibition constant
Kₘ  Michaelis-Menten constant
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{ow}$</td>
<td>octanol–water partition coefficient</td>
</tr>
<tr>
<td>LC</td>
<td>liquid chromatography</td>
</tr>
<tr>
<td>LD</td>
<td>lactational day</td>
</tr>
<tr>
<td>LD$_{50}$</td>
<td>median lethal dose</td>
</tr>
<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
</tr>
<tr>
<td>LH</td>
<td>luteinizing hormone</td>
</tr>
<tr>
<td>LOAEL</td>
<td>lowest-observed-adverse-effect level</td>
</tr>
<tr>
<td>LOD</td>
<td>limit of detection</td>
</tr>
<tr>
<td>LOEL</td>
<td>lowest-observed-effect level</td>
</tr>
<tr>
<td>LOQ</td>
<td>limit of quantification</td>
</tr>
<tr>
<td>LOR</td>
<td>limit of reporting</td>
</tr>
<tr>
<td>LRMS</td>
<td>low-resolution mass spectrometry</td>
</tr>
<tr>
<td>LTP</td>
<td>long-term potentiation</td>
</tr>
<tr>
<td>MAE</td>
<td>microwave-assisted extraction</td>
</tr>
<tr>
<td>MAP</td>
<td>mitogen-activated protein</td>
</tr>
<tr>
<td>MEK</td>
<td>mitogen-activated protein kinase</td>
</tr>
<tr>
<td>MeO</td>
<td>methoxy</td>
</tr>
<tr>
<td>ML</td>
<td>maximum level</td>
</tr>
<tr>
<td>MOE</td>
<td>margin of exposure</td>
</tr>
<tr>
<td>MPO</td>
<td>medial preoptic area</td>
</tr>
<tr>
<td>mRNA</td>
<td>messenger ribonucleic acid</td>
</tr>
<tr>
<td>MROD</td>
<td>7-methoxyresorufin O-deethylase</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio</td>
</tr>
<tr>
<td>N1-GA-dA</td>
<td>N1-(2-carboxy-2-hydroxyethyl)-2'-deoxyadenosine</td>
</tr>
<tr>
<td>N3-GA-Ade</td>
<td>N3-(2-carbamoyl-2-hydroxyethyl)adenine</td>
</tr>
<tr>
<td>N$_{6}$-GA-dA</td>
<td>$N_{6}$-(2-carboxy-2-hydroxyethyl)-2'-deoxyadenosine</td>
</tr>
<tr>
<td>N7-GA-Gua</td>
<td>N7-(2-carbamoyl-2-hydroxyethyl)guanine</td>
</tr>
<tr>
<td>NA</td>
<td>not available; not analysed</td>
</tr>
<tr>
<td>NADH</td>
<td>nicotinamide adenine dinucleotide, reduced form</td>
</tr>
<tr>
<td>NADPH</td>
<td>nicotinamide adenine dinucleotide phosphate, reduced form</td>
</tr>
<tr>
<td>NAT</td>
<td>N-acetyltransferase</td>
</tr>
<tr>
<td>NCV</td>
<td>nerve conduction velocity</td>
</tr>
<tr>
<td>ND</td>
<td>not detected</td>
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<tr>
<td>NHL</td>
<td>non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health (USA)</td>
</tr>
<tr>
<td>NK</td>
<td>natural killer</td>
</tr>
<tr>
<td>NMA</td>
<td>N-methylolacrylamide</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>nNOS</td>
<td>neural nitric oxide synthase</td>
</tr>
<tr>
<td>NOAEL</td>
<td>no-observed-adverse-effect level</td>
</tr>
<tr>
<td>NOEL</td>
<td>no-observed-effect level</td>
</tr>
<tr>
<td>NPD</td>
<td>nitrogen–phosphorus detection</td>
</tr>
<tr>
<td>NQ</td>
<td>not quantified</td>
</tr>
<tr>
<td>NTP</td>
<td>National Toxicology Program (USA)</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>OH</td>
<td>hydroxy</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>PAH</td>
<td>polycyclic aromatic hydrocarbon</td>
</tr>
<tr>
<td>PBB</td>
<td>polybrominated biphenyl</td>
</tr>
<tr>
<td>PBDD</td>
<td>polybrominated dibenzo-p-dioxin</td>
</tr>
<tr>
<td>PBDE</td>
<td>polybrominated diphenyl ether</td>
</tr>
<tr>
<td>PBDF</td>
<td>polybrominated dibenzofuran</td>
</tr>
<tr>
<td>PBPK</td>
<td>physiologically based pharmacokinetic</td>
</tr>
<tr>
<td>PCB</td>
<td>polychlorinated biphenyl</td>
</tr>
<tr>
<td>PCDD</td>
<td>polychlorinated dibenzo-p-dioxin</td>
</tr>
<tr>
<td>PCDE</td>
<td>polychlorinated diphenyl ether</td>
</tr>
<tr>
<td>PCDF</td>
<td>polychlorinated dibenzofuran</td>
</tr>
<tr>
<td>PCE</td>
<td>polychromatic erythrocyte</td>
</tr>
<tr>
<td>PCNA</td>
<td>proliferating cell nuclear antigen</td>
</tr>
<tr>
<td>PFC</td>
<td>plaque-forming cell</td>
</tr>
<tr>
<td>PKC</td>
<td>protein kinase C</td>
</tr>
<tr>
<td>PLA2</td>
<td>phospholipase A2</td>
</tr>
<tr>
<td>PMTDI</td>
<td>provisional maximum tolerable daily intake</td>
</tr>
<tr>
<td>PND</td>
<td>postnatal day</td>
</tr>
<tr>
<td>ppm</td>
<td>part per million</td>
</tr>
<tr>
<td>ppt</td>
<td>part per trillion</td>
</tr>
<tr>
<td>PR</td>
<td>progesterone receptor</td>
</tr>
<tr>
<td>PROD</td>
<td>7-pentoxyresorufin O-depentylase</td>
</tr>
<tr>
<td>PTWI</td>
<td>provisional tolerable weekly intake</td>
</tr>
<tr>
<td>PTWI_d</td>
<td>daily equivalent of the provisional tolerable weekly intake</td>
</tr>
<tr>
<td>QA</td>
<td>quality assurance</td>
</tr>
<tr>
<td>QC</td>
<td>quality control</td>
</tr>
<tr>
<td>QSAR</td>
<td>quantitative structure–activity relationship</td>
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<tr>
<td>RIVM</td>
<td>National Institute of Public Health and the Environment (Netherlands)</td>
</tr>
<tr>
<td>RIVO</td>
<td>Netherlands Institute of Fisheries Research</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>SAR</td>
<td>Special Administrative Region</td>
</tr>
<tr>
<td>s.c.</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>SCOOP</td>
<td>Scientific Cooperation on Food</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SFE</td>
<td>supercritical fluid extraction</td>
</tr>
<tr>
<td>SIM</td>
<td>selected ion monitoring</td>
</tr>
<tr>
<td>SMR</td>
<td>standardized mortality ratio</td>
</tr>
<tr>
<td>SPE</td>
<td>solid-phase extraction</td>
</tr>
<tr>
<td>SRM</td>
<td>selective-reaction monitoring</td>
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<tr>
<td>T3</td>
<td>triiodothyronine</td>
</tr>
<tr>
<td>T4</td>
<td>thyroxine</td>
</tr>
<tr>
<td>TBG</td>
<td>thyroxine binding globulin</td>
</tr>
<tr>
<td>TCDD</td>
<td>2,3,7,8-tetrachlorodibenzo-p-dioxin</td>
</tr>
<tr>
<td>TD50</td>
<td>chronic dose that results in one half of animals developing tumours</td>
</tr>
<tr>
<td>TDS</td>
<td>Total Diet Study</td>
</tr>
<tr>
<td>TEF</td>
<td>toxic equivalency factor</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>TGF</td>
<td>transforming growth factor</td>
</tr>
<tr>
<td>TLC</td>
<td>thin-layer chromatography</td>
</tr>
<tr>
<td>TPA</td>
<td>tetradecanoyl-phorbol acetate</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
</tr>
<tr>
<td>TT3</td>
<td>total triiodothyronine</td>
</tr>
<tr>
<td>TT4</td>
<td>total thyroxine</td>
</tr>
<tr>
<td>TTC</td>
<td>threshold of toxicological concern</td>
</tr>
<tr>
<td>TTR</td>
<td>transthyretin</td>
</tr>
<tr>
<td>UDPGT</td>
<td>uridine diphosphate glucuronosyltransferase</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>US EPA</td>
<td>United States Environmental Protection Agency</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>Val</td>
<td>valine</td>
</tr>
<tr>
<td>$V_d$</td>
<td>volume of distribution</td>
</tr>
<tr>
<td>$V_{max}$</td>
<td>maximum rate of metabolism</td>
</tr>
<tr>
<td>VMH</td>
<td>ventromedial hypothalamic nucleus</td>
</tr>
<tr>
<td>v/v</td>
<td>volume by volume</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>w/w</td>
<td>weight by weight</td>
</tr>
</tbody>
</table>
ANNEX 3

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

Rome, 8–17 February 2005

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Mrs I. Meyland, Senior Scientific Adviser, Danish Institute of Food and Veterinary Research, Søborg, Denmark (Vice-Chairperson)

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ANNEX 4

THE FORMULATION OF ADVICE ON COMPOUNDS THAT ARE BOTH GENOTOXIC AND CARCINOGENIC

The Committee has established procedures for determining health-based guidance values, such as the acceptable daily intake (ADI) or provisional tolerable weekly intake (PTWI), for chemicals that produce adverse effects that are thought to show a threshold in their dose–response relationships. Compounds that are both genotoxic and carcinogenic may show non-linear dose–response relationships, but the no-observed-effect level (NOEL) in a study of carcinogenicity represents the limit of detection in that bioassay, rather than an estimate of a possible threshold. Therefore, the Committee does not establish health-based guidance values for compounds that are genotoxic and carcinogenic using the NOEL and safety (uncertainty) factors. In the absence of evidence on the influence of non-linearity on the incidence of cancer at low levels of exposure, the advice given previously by the Committee for compounds that are both genotoxic and carcinogenic has been that intakes should be reduced to as low as reasonably achievable (ALARA). Such advice is of limited value, because it does not take into account either human exposure or carcinogenic potency and has not allowed risk managers to prioritize different contaminants or to target risk management actions. In addition, ever-increasing analytical sensitivity means that the number of chemicals with both genotoxic and carcinogenic potential detected in food will increase.

The Committee at its present meeting considered a number of compounds for which genotoxicity and carcinogenicity are important issues. The Committee was aware of a number of recent developments relevant to the risk assessment of such compounds, including:

— a WHO workshop that developed a strategy for dose–response assessment and the formulation of advice (1);

— discussions within the European Food Safety Authority about a margin of exposure (MOE) that would indicate the level of priority for risk management action (2); and

— Australian recommendations for genotoxic and carcinogenic soil contaminants regarding a guideline dose that would be protective of human health based on a modified benchmark dose and the application of uncertainty factors to allow for interspecies differences, intraspecies variability, quality of the database and the seriousness of the carcinogenic response (3).

1 Taken from section 2.1 of the Sixty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives (see Annex 1, reference 174).
The Committee discussed approaches to the formulation of advice on contaminants that are both genotoxic\(^1\) and carcinogenic, which would inform risk managers about the possible magnitude of health concerns at different levels of intake in humans.

Hazard identification would normally be based on data from studies on genotoxicity and from cancer bioassays. Some chemicals increase the incidence of cancer in experimental animals by non-genotoxic mechanisms, and establishing a health-based guidance value, such as a PTWI, would be appropriate. The present guidance relates to chemicals that are both genotoxic and carcinogenic.

Hazard characterization (dose–response assessment) would be based on the available dose–response data for cancer, which would mostly be derived from studies in rodents given daily doses many orders of magnitude greater than the estimated intakes in humans. Dose–response data from studies of epidemiology may also be used for hazard characterization and would avoid interspecies comparisons and extrapolation over many orders of magnitude. The recent WHO workshop recommended the use of the benchmark dose lower confidence limit (BMDL) as a starting point for hazard characterization based on data from a bioassay for cancer in animals when the data are suitable for dose–response modelling. The BMDL is the lower one-sided confidence limit of the benchmark dose (BMD) for a predetermined level of response, called the benchmark response (BMR), such as a 5% or 10% incidence. The BMD in most cases shows less variation than the BMDL for different mathematical models and may be more suitable for ranking different compounds in terms of their potency, while the BMDL may be more appropriate for risk characterization purposes because it reflects the quality of the data. The derivation and interpretation of a BMDL require considerable statistical and biological expertise.

A number of aspects of the database need to be considered in dose–response modelling, including data selection, model selection, statistical linkage, parameter estimation, implementation and evaluation (\(f\)). The dose metric used for modelling could be a biomarker, providing that it was critically related to the process by which cancer arises and had been validated in relation to the external dose or intake. For carcinogenesis, selection of the dose–response data for modelling will need to consider both site-specific incidences of tumours, especially for the site showing the greatest sensitivity, and combined data (e.g. numbers of tumour-bearing animals) for compounds that do not show clear organ specificity. Analyses based on the numbers of tumour-bearing animals may also be

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\(^1\) The present guidance does not address the situation where a compound shows genotoxicity, or has structural alerts for genotoxicity, but where a bioassay for cancer has not been performed. The Committee is aware of developments, such as the threshold of toxicological concern (TTC) for compounds with structural alerts for genotoxicity, that may allow the formulation of limited advice to risk managers, and would welcome a critical evaluation of such approaches.
appropriate under other circumstances, for example in the assessment of complex mixtures of compounds that are both genotoxic and carcinogenic. Dose–response characterization should aim to define the BMDL for the carcinogenic response(s) of relevance to human health, at the lowest level of response (the BMR) that reliably defines the lower end of the observed experimental dose–response relationship. A BMR of a 10% incidence is likely to be the most appropriate for modelling of data from bioassays for cancer, because the values for different mathematical models show wider divergence at incidences below 10%. The consistent use of the same benchmark response, i.e. 10%, will facilitate comparisons of the risks associated with different compounds that are both genotoxic and carcinogenic. Non-cancer effects produced by compounds that are both genotoxic and carcinogenic may be analysed using the same approach, and comparison of the derived BMDL values and their associated slopes can help to identify the adverse effect that is critical to risk assessment of the compound.

The intake (exposure) assessment for a compound that is both genotoxic and carcinogenic is no different from that for other types of contaminants.

Risk characterization involves comparison of the estimated exposure with the identified BMDL. In principle, this can take different forms:

- **Calculation of the margin of exposure (MOE, the ratio of the BMDL to the estimated intake in humans).** The MOE can be used to prioritize different contaminants, providing that a consistent approach has been adopted. The acceptability of an MOE depends on its magnitude and is ultimately a risk management decision (1). To aid that decision, the risk assessor should provide information on the nature and magnitude of uncertainties in both the toxicological and exposure data. Although the risk assessor should not provide an assessment of the acceptability of the MOE, guidance should be given on its adequacy taking into account the inherent uncertainties and variability.

- **Dose–response analysis outside the observed dose range.** Quantitative dose–response analysis could be used to calculate the incidence of cancer that is theoretically associated with the estimated exposure for humans, or the exposure associated with a predetermined incidence (e.g. 1 in 1 million). In order to provide realistic estimates of the possible carcinogenic effect at the estimated exposure for humans, mathematical modelling would need to take into account the shape of the dose–response relationship for the high doses used in the bioassay for cancer and for the much lower intakes by humans. Such information cannot be derived from the available data on cancer incidence from studies in animals. In the future, it may be possible to incorporate data on dose–response or concentration–response relationships for the critical biological activities involved in the generation of cancer (e.g. metabolic bioactivation and detoxication processes, DNA binding, DNA repair, rates of cell proliferation and apoptosis) into a biologically based dose–response model for cancer that would also incorporate data on species differences in these processes. However, such data are not currently
available. At present, any estimate of the possible incidence of cancer in experimental animals at intakes equal to those for humans has to be based on empirical mathematical equations that may not reflect the complexity of the underlying biology. A number of mathematical equations have been proposed for extrapolation to low doses. The resulting risk estimates are dependent on the mathematical model used; the divergence increases as the dose decreases, and the output by different equations can differ by orders of magnitude at very low incidences.

- **Linear extrapolation from a point of departure.** Because the estimated risks at low doses are model-dependent, linear extrapolation from the BMDL, which is conservative and simple to apply, has been used as a matter of policy by some agencies in order to calculate levels of exposure associated with different theoretical incidences of cancer. The incidence used is regarded as an upper-bound estimate for lifetime risk of cancer, and the actual risk may lie anywhere between zero and the calculated upper-bound estimate. Calculation of the intake associated with an incidence of 1 in 1 million from the BMDL for a 10% incidence using linear extrapolation is simply equivalent to dividing the BMDL by 100,000, and this approach is therefore no more informative than calculation of an MOE.

Of the three options given above, the MOE and linear extrapolation from a point of departure are the most pragmatic and usable at the present time. Linear extrapolation from a point of departure offers no advantages over an MOE, and the results are open to misinterpretation because the numerical estimates may be regarded as quantification of the actual risk.

The Committee at its present meeting decided that advice on compounds that are both genotoxic and carcinogenic should be based on estimated MOEs. The strengths and weaknesses inherent in the data used to calculate the MOE should be given as part of the advice to risk managers, together with advice on its interpretation.

**References**


ANNEX 5

APPROACH TO DOSE–RESPONSE MODELLING

At the present meeting, cancer dose–response data were analysed by dose–response modelling, in accordance with the International Programme on Chemical Safety (IPCS) document Principles for modelling dose–response for the risk assessment of chemicals (1). The statistical methods of dose–response modelling as applied at this meeting are briefly described below.

For each tumour end-point considered relevant, the quantal dose–response models given in Table 1 were fitted to the dose–incidence data:

<table>
<thead>
<tr>
<th>Model</th>
<th>Model equation</th>
<th>Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-stage</td>
<td>$R = a + (1-a)(1-\exp(-x/b))$</td>
<td>$0 \leq a \leq 1$,</td>
</tr>
<tr>
<td>Two-stage</td>
<td>$R = a + (1-a)(1-\exp(-(x/b)-c(x/b)^2))$</td>
<td>$0 \leq a \leq 1$</td>
</tr>
<tr>
<td>Log-logistic</td>
<td>$R = a+(1-a)/(1+\exp(c \log10(b/x)))$</td>
<td>$0 \leq a \leq 1$, c ≥ log(10)</td>
</tr>
<tr>
<td>Log-probit</td>
<td>$R = a+(1-a) \Phi(c \log10(x/b))$</td>
<td>$0 \leq a \leq 1$</td>
</tr>
<tr>
<td>Weibull</td>
<td>$R = a + (1-a)(1-\exp(-(x/b)^c))$</td>
<td>$0 \leq a \leq 1$, c &gt; 1</td>
</tr>
<tr>
<td>Proast M2</td>
<td>$y = \exp(bx)$, $th1$</td>
<td></td>
</tr>
<tr>
<td>Proast M3</td>
<td>$y = \exp(b x^d)$, $th1$</td>
<td>$d \geq 1$</td>
</tr>
<tr>
<td>Proast M4</td>
<td>$y = c - (c-1)\exp(-bx)$, $th1$</td>
<td></td>
</tr>
</tbody>
</table>

$\Phi$ denotes the (cumulative) standard normal distribution function.

The first five of these models directly relate the incidence ($R$, expressed as a fraction) to the dose ($x$). In these models, the parameter $a$ (also expressed as a fraction) reflects the incidence in the controls, the parameter $b$ denotes the slope parameter $c$ can be considered as a shape parameter. The last three models (Proast M2–M4) are a specific family of models that assume an underlying continuous response (indicated by $y$), which is translated into a binary response

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1 Taken from Annex 3 of the Sixty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives (see Annex 1, reference 174).
(incidence) by incorporating a cut-off point \((th_1)\) in the normal distribution around \(y\), below which an animal does not respond, and above which it does respond.

Some of the models are nested members of a larger family of models. Two models are nested when the one model can be seen as an extension of the other (simpler) model by incorporating one or more parameters. For instance, the two-stage model is an extension of the one-stage model by including parameter \(c\). Also, the Proast models are a nested family of models (2). Nested models can be formally compared with each other as follows. Inclusion of an extra model parameter should result in a higher log-likelihood value, and if this increase is \(>1.92\), inclusion of the parameter has resulted in a significantly better fit (log-likelihood ratio test). If the increase is \(<1.92\), the fit is not significantly better, and the parameter is omitted.

When dose–response data are available from more than one study, or for both sexes, these models are fitted simultaneously to both such subgroups. This was done either by assuming all parameters in the model being the same for all subgroups or by assuming only the background response parameter \((a)\) being different, or only the slope \((b)\). When all parameters are assumed to be the same, a single curve results, otherwise different curves for the subgroups will result. A model in which a parameter is assumed to be different represents a model that is nested to the same model with the parameter assumed the same for the subgroups. Hence, the log-likelihood ratio test can be used for testing if an additional background or slope parameter results in a significantly better fit.

**Selection of models**

In general, those models that do not result in a significantly worse fit than the saturated model (one parameter per data point) are considered to be acceptable. For instance, when the saturated model has eight parameters (i.e. eight observed incidences available), a fitted dose–response model with three parameters should result in a log-likelihood that is no more than 5.54 lower than the log-likelihood associated with the saturated model. Table 2 summarizes the critical differences in log-likelihood values for various numbers of degrees of freedom (= difference in number of parameters between the models to be compared).

For those models that were considered acceptable according to the criteria mentioned, the benchmark dose (BMD) values as well as the benchmark dose lower confidence limit (BMDL) values were calculated. All BMD and BMDL values were calculated for a 10% extra risk, defined as:

\[
\text{extra risk} = \frac{R(\text{BMD}) - R(0)}{1 - R(0)}
\]

This represents the additional-response fraction divided by the tumour-free fraction in the controls.
Table 2. Critical differences in log-likelihood values making an increase by a number of parameters (= number of degrees of freedom) to result in a significantly better fit

<table>
<thead>
<tr>
<th>Number of degrees of freedom</th>
<th>Critical difference in log-likelihood ((\alpha = 0.05))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.92</td>
</tr>
<tr>
<td>2</td>
<td>3.00</td>
</tr>
<tr>
<td>3</td>
<td>3.91</td>
</tr>
<tr>
<td>4</td>
<td>4.74</td>
</tr>
<tr>
<td>5</td>
<td>5.54</td>
</tr>
<tr>
<td>6</td>
<td>6.30</td>
</tr>
<tr>
<td>7</td>
<td>7.03</td>
</tr>
<tr>
<td>8</td>
<td>7.75</td>
</tr>
</tbody>
</table>

The BMD and BMDL values were estimated by the bootstrap method, usually performing 500 bootstrap runs. These values therefore contain some random error, but usually no more than about 10% for the BMDL.

The calculations were performed using the dose–response software package PROAST, version V07 (developed at the National Institute of Public Health and the Environment [RIVM], Bilthoven, The Netherlands), which is freely available.

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