COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Second Draft of COC Guidance Statement G05: Defining a Point of Departure and Potency Estimates in Carcinogenic Dose Response

1. This paper was prepared by the PHE Toxicology Unit, Imperial College London, and a second draft of the Committee Guidance Statement on Points of Departure and Potency Estimates is presented in Annex A.

2. The revised first draft was brought to the November COC meeting. It was agreed that the members would provide written comments on certain aspects. The revised paper with tracked changes incorporates comments received from members at the meeting and by correspondence. The Secretariat would like Member's views on the overall content of the revised statement. Specific guidance are requested on the areas outlined below.

3. Paragraph 15 describes the TD50 methodology for potency ranking of carcinogens. For completeness, an overall view of Members on TD50 is sought. Previously this Committee has concluded that the TD50 is a practical quantitative estimate of carcinogenic potency for the ranking of genotoxic carcinogens. Does this view still hold?

4. T25 approach has been used in risk assessment for regulation of non-food, genotoxic carcinogenic chemicals in the EU (EFSA, 2006) (paragraph 21). From our notes of the November COC meeting, Members do not agree that T25 should be used in risk assessment. Have the recent developments of BMD led to this opinion?

5. Paragraph 37 describes further developments of the TTC decision tree. These include further refinements of the TTC decision tree proposed by Felter et al. in 2009, including consideration for chemicals that have structural alerts for genotoxicity but negative data from genotoxicity tests. They proposed using a higher threshold value of 1.5 µg/person/day as an appropriate TTC exposure limit in such cases. In addition, approaches for use in cases where exposure is going to be for periods up to one year are suggested. Further clarification of Members views on these are sought as well as an overall view of Members on the TTC decision tree. Members may wish to acknowledge these developments but for practical application, exercise careful consideration on a case-by-case basis.

6. Members have requested a glossary of terms to be included in the G05 statement. This is attached in Annex B. Members should note that an overall glossary will be provided for guidance statements in due course.

COC Secretariat
February 2014

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

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This Annex, prepared by the PHE Toxicology Unit, Imperial College London, contains the second draft of the COC Guidance Statement G05: Defining a Point of Departure and Potency Estimates in Carcinogenic Dose Response

Note: This is a draft guidance statement for discussion. It does not represent the final view of the Committee and should not be quoted, cited or reproduced.

COC Secretariat
February 2014

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

COC Guidance Statement G05: Second Draft

Introduction

1. This guidance statement provides an overview of the various methods for deriving points of departure and potency estimates associated with exposures to chemical carcinogens. It is part of a series of guidance statements by the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. It should be read in conjunction with these, in particular G01 on the overall strategy of risk assessment of chemical carcinogenicity, G02[1] on the interpretation of evidence of carcinogenicity in humans, G03[2] on hazard identification and characterisation and G06 on risk characterisation methods.

2. This guidance document describes how to derive points of departure (POD) and potency estimates ~~such as~~including the Benchmark Dose (BMD), T25, and TD50 ~~,~~ and ~~the BMD and~~ describes how they can be used to estimate the relative potency of genotoxic carcinogens. However, amongst these, the BMD is the most widely preferred POD approach and the COC recommends its use.. Similarly in recent times, the BMDL is the preferred POD ~~point of departure~~ for thesholded non-genotoxic carcinogens. However, in certain situations, such as when it is not possible to apply the BMD methodology, the traditional approach of the no-observed adverse effect level (NOAEL) can be adopted for non-genotoxic compounds. Indeed, this approach can be used for genotoxic carcinogens, although it would be important that use of a "NOAEL" in such cases does not necessarily imply the existence of a threshold in the dose-response relationship. ~~including: No-observed adverse effect level (NOAEL), Benchmark Dose (BMD), T25 and TD50, associated with exposures to chemical carcinogens.~~ This guidance document also details t~~T~~he Threshold of Toxicological Concern (TTC) approach which can~~also~~ help to identify priorities for more detailed carcinogenicity evaluation, particularly for chemicals not subject to regulatory approval schemes.~~It is part of a series of guidance statements by the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. It should be read in conjunction with these, in particular G01 on the overall strategy of risk assessment of chemical carcinogenicity, G02[3] on the interpretation of evidence of carcinogenicity in humans, G03[4] on hazard identification and characterisation and G06 on risk characterisation methods.~~

3. Hazard characterisation involves a qualitative description of the nature of the hazard and a quantitative description of the change in effect caused by differing doses of a chemical substance after a certain exposure time i.e. the dose-response relationship. The purpose of analysing the dose-response relationship is to

1 This G02 guidance has yet to be published, at time of writing G05, February 2014
2 This G03 guidance has yet to be published, at time of writing G05, February 2014

investigate the magnitude of response (in terms of severity or incidence) within the dose range used in an animal study or within the range of exposures experienced in a human study. This helps to estimate the response and, ultimately, the risk from exposure to the concentrations of the chemical in the environment, food etc. These are usually much lower than those used in animal studies and often also lower than those to which individuals have been exposed in human studies. The relationship between dose and response may be used to aid hazard characterisation by allowing a comparison of carcinogenic potency. Carcinogenic potency estimates give an indication of the dose of a substance administered over a standard animal lifespan that results in a fixed incidence of tumours, such as, 5, 25 or 50%, after correction for the spontaneous background incidence of tumours among controls (Barlow et al., 2006). However, other important factors that can affect this relationship in humans, and should be further considered, are species differences in absorption, distribution, metabolism and excretion (ADME), mode of action and variability in susceptibility between species and within humans.

4. There are a number of methods for the characterisation of hazard due to the carcinogenicity of genotoxic compounds. In all of these, chemicals are classified with regard to tumourigenicity on the basis of potency. In this context, potency is ideally represented by the overall position and shape of the dose-effect or dose-response curve, but the value (dose) at a particular point on the curve (~~point of departure or~~ POD) is often used as a surrogate. The POD~~. This is known as the point of departure, which~~ is the dose associated with a specified level of effect or response that can be determined from dose-response data from a study. An example is the dose level associated with a tumour incidence that is 10% above the incidence in the control group. The Committee recognises that, where data on tumourigenicity *per se* are lacking, it may be possible to use continuous data as a surrogate measure of response, such as specific DNA damage observed in target organs, for determining a point of departure.
~~This guidance document describes how to derive points of departure such as T25, TD50, and the BMD and describes how they can be used to estimate the relative potency of genotoxic carcinogens. However, amongst these, the BMD is the most widely preferred. Similarly in recent times, the BMD is the preferred point of departure for thesholded non-genotoxic carcinogens. However, in certain situations, such as when it is not possible to apply the BMD methodology, the traditional approach of the no-observed adverse effect level (NOAEL) can be adopted for non-genotoxic compounds. Indeed, this approach can be used for genotoxic carcinogens, although it would be important that use of a "NOAEL" in such cases does not necessarily imply the existence of a threshold in the dose-response relationship. The Threshold of Toxicological Concern (TTC) approach can also help to identify priorities for more detailed carcinogenicity evaluation, particularly for chemicals not subject to regulatory approval schemes.~~
5. It should be noted that there is no difference in the methodology used for determining points of departure for genotoxic and non-genotoxic carcinogens. It is how the dose-response relationship and the point of departure are used in the final assessment of risk that varies, depending on whether or not a carcinogenic response occurs through a genotoxic or non-genotoxic mode of action (see Guidance Document G06 for further discussion of Risk Characterisation).

Points of Departure and Potency Estimates

Benchmark Dose (BMD) approach

6. The Benchmark Dose (BMD) methodology was initially introduced by Crump (1984) as an alternative to the use of NOAELs and LOAELs in dose–response assessment for setting regulatory levels such as reference doses (RfDs), reference concentrations (RfCs) and acceptable daily intakes (ADIs) for effects for which it is assumed there is a threshold, and subsequently further developed within the US EPA (US EPA, 1995). Both EFSA and WHO recommend the BMD approach for deriving a point of departure (POD) (also known as a reference point) to be used as a starting point for human health risk assessment, for all endpoints, including carcinogenicity by a genotoxic mode of action. The BMD approach ~~is a scientifically superior method~~has a number of advantages over ~~to~~ the NOAEL approach. ~~, since it~~ The BMD approach makes more complete use of the available dose–response data, it takes into account the shape of the dose-response curve more explicitly and it is less dependent on dose spacing. It also~~and it~~ enables quantification of the uncertainties in the dose-response data using statistical methodology ~~, amongst other advantages~~ (EFSA, 2009).

7. The BMDx is defined as the dose that corresponds to a specific change (x %) in response compared to the (modelled) response in control animals, the benchmark response (BMR) (Crump, 1995). The BMD is determined by fitt~~modell~~ing a mathematical curve to the dose-response data over the range of observable responses from animal or human (if available) studies, using a selection of different models. From each statistically acceptable modelled dose–response curve, a value for the BMD is obtained (see paragraph 12 and 13 on how to choose the most appropriate BMD). To take experimental uncertainty into account, the lower 95% confidence bound on the benchmark dose (BMDLx) is used as the POD. Figure 1 illustrates the BMD approach.

8. Both dichotomous data and continuous data from animal and human dose response studies can be evaluated using the BMD approach (EFSA, 2009). Dichotomous (quantal or incidence) data describe whether an effect has occurred in an individual or not, e.g., presence of tumour, death. The data obtained from carcinogenicity studies fall into the dichotomous category. Continuous data are typically quantitative measurements or a contrast (absolute change from control or relative change from control). The analysis of human dose-response data is generally more complicated than that of animal dose-response due to the presence of confounders and imprecision in the exposure estimates (EFSA, 2009). For the purpose of this guidance statement on defining a POD in a carcinogenic dose response, only considerations of quantal data will be discussed, though it is acknowledged that effects such as DNA damage would need to use an approach appropriate for continuous data.

9. Before a dataset is analysed using the BMD methodology, it is necessary to evaluate all available studies and potential critical effects, ensuring that the datasets meet minimum criteria, as outlined in the EFSA opinion (2009). There are two aspects here, and in part they depend on the BMD approach to be used. One is selection of tumour-response data relevant to risk assessment of a genotoxic carcinogen and the other is ensuring a data set is suitable for modelling. In the

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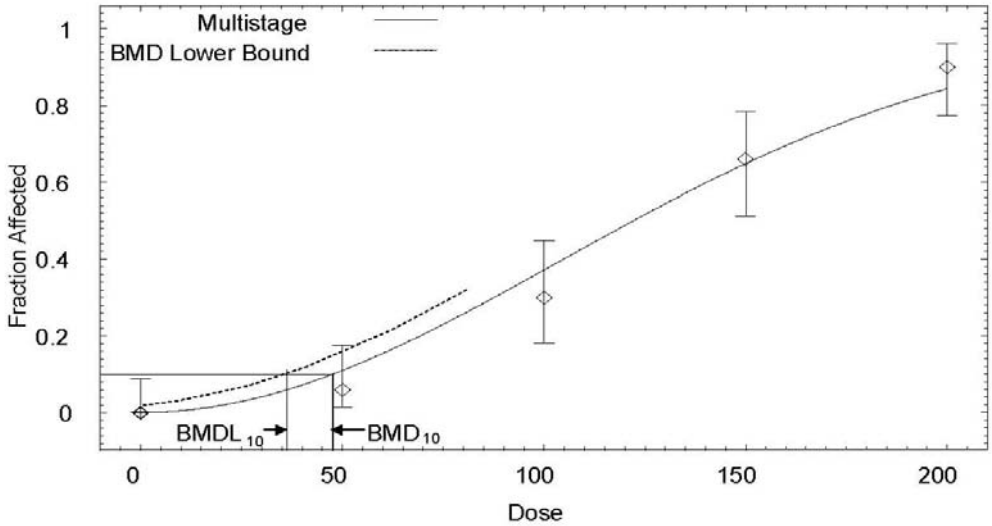
BMD approach, one might model all suitable datasets or combinations thereof (accepting the need for caution in combining data) and then interpret the resulting BMDLs, or one may choose to model only what is considered to be the critical data set, the one likely to give the most conservative outcome from amongst those that are considered relevant. Once an appropriate dataset is chosen, BMD analysis involves a number of steps including the choice of BMR, model selection, model fit assessment and data reporting.



~~**Figure 1: Key concepts for the BMD approach.** The plotted graphs represent estimates of extra risk at each dose. The solid curve is a fitted dose-response model. This curve determines the BMD (point estimate), which is generally defined as a dose that corresponds to a low but measurable change in response, denoted the BMR, in this example, 10% extra risk. The dashed curve represents the lower (one-sided) 95% confidence limit of the fitted dose-response model. (Taken from Bedford et alet al, 2010).~~**Figure 1. Example of a model fit to dichotomous data, with BMD and BMDL indicated.** The fraction of animals affected in each group is indicated by diamonds, and the error bars indicate 95% confidence intervals for the fraction affected. The BMR in this example is an extra risk of 10% (or 0.1 fraction responding). The fitted model is shown by the solid curve, and the BMD corresponding to 10% extra risk on this curve is notated BMD10. The lower bound on BMD10, notated BMDL10, comes from the dashed curve to the left of the fitted model curve, indicating the estimated lower bound on doses for a range of BMRs (taken from US EPA technical document, 2012).

10. For quantal responses, the BMR is expressed in terms of a percent increase in risk[5] of adverse outcome above the modelled background. The BMR is typically set at the lower end of the range of responses that can be detected experimentally, or the observations in epidemiological studies. EFSA (2009) recommend that a default BMR value of 10% be used for quantal data from a guideline rodent carcinogenicity study, since the modelling of lower responses generally results in greater uncertainty. Based on statistical and toxicological considerations, a modified BMR can be used, for example a BMR of 1% has been used with epidemiological studies of large populations (US EPA, 2000 and EFSA 2009).

5 This can be expressed as 'extra' risk (the default in BMDS) or as 'added' risk. The BMR is calculated differently, depending on which risk type is chosen.

11. Both the WHO/IPCS and EFSA have produced guidance on dose–response modelling, including guidance on cancer dose-response data (WHO/IPCS (2009) and EFSA, 2009). Table 1 lists the recommended models for BMD analysis for quantal data. It should be noted that the models outlined in the table may change over time and are therefore not exhaustive of all models that could be used. Different models that fit the data equally well, as judged by statistical comparison, can result in different BMDs and BMDLs, reflecting model uncertainty. The selection of the group of models to investigate is dependent on the endpoint being modelled (quantal or continuous) and the experimental design used to generate the data (e.g. number of dose groups utilised and nested study design (Davis et al., 2011)). The US EPA technical guidance document (2012) and the EFSA guidance (2009) both detail the various models that can be used in BMD modelling with existing software. Model selection and model constraints are important considerations in BMD estimation. The main option in model selection for BMD estimation using quantal data is the choice of model classes (Sand et al., 2008).

Table 1. Recommended models for use in the BMD approach[3] (taken from EFSA, 2009)

Model	**Number of model parameters**	**Model expression response (*y*) as function of dose (*x*)**	**Constraints**
		Quantal data [1]	
Logistic	2	y = 1 / (1 + exp(-a – bx))	b>0
Probit	2	y = CumNorm(a + bx)	b>0
Log-logistic	3	y = a + (1-a) / (1 + exp(-log(x/b)/c))	$0 \le a \le 1$, b>0, c>1
Log-probit	3	y = a + (1-a) CumNorm(log(x/b)/c)	$0 \le a \le 1$, b>0, c>0
Weibull	3	y = a + (1-a) exp($(x/b)^c$)	$0 \le a \le 1$, b>0, c>1
Gamma	3	y = a + (1-a) CumGam(bx^c)	$0 \le a \le 1$, b>0, c>1
		Linearized multistage (LMS) family [2]	
One-stage	2	y = a + (1-a) exp(– bx)	a>0, b>0
Two-stage	3	y = a + (1-a) exp(– bx – cx^2)	a>0, b>0, c>0
Three-stage	4	y = a + (1-a) exp(– bx – cx^2 – dx^3)	a>0, b>0, c>0, d>0

a, b, c, d : unknown parameters that are estimated by fitting the model to the data.
CumNorm: cumulative (standard) normal distribution function.
CumGam: cumulative Gamma distribution function.
[1] For the constraints given here, the models result in increasing dose-response curves.
[2] The one-stage model is identical to the quantal linear model as implemented in BMDS; note that in BMDS, this model is called “multistage” and the number of stages has to be defined by setting the degree of the polynomial in this moel, e.g. 2 for a two-stage model.
[3] In epidemiology, additional models, e.g. y=a+bx, are also used. (EFSA, 2009).

12. Once the selected models have been fitted to the data, a series of scientific judgements must be made to ensure the fitted models adequately describe the

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data. Different types of statistical testing can be utilised to assess the adequacy of model fit. For model selection, an important criterion is that the selected model should adequately describe the data, especially in the region of the BMR. EFSA guidance for model fit involves two principles: deciding which model fits best within a nested family of increasingly complex models, where this is necessary, and then a determination of overall goodness-of-fit. Both principles are based on likelihood ratio test and EFSA recommends a minimum goodness of fit value of p = 0.05 for model acceptance. For dichotomous data, the U.S. EPA software employs the Pearsons chi-squared goodness of fit test (US EPA, 1995). The US EPA (2012) recommend a minimum goodness of fit p value of p = 0.1 for model acceptance. Akaike information criterion (AIC) value, which is a measure of the degree of fit weighted by the number of free parameters in the model and/or Pearsons Chi-squared can also be used for selection within a nested series. There is a complication when multiple dose groups are available. A scenario may exist where no model gives an acceptable fit but visually one or more curves appear to provide an adequate description of the data. EFSA and others have suggested that it may be appropriate to use a lower p-value for the likelihood ratio test in such circumstances or, if there are still no statistically acceptable models, to accept such models anyway.

13. It is often the case that a number of models will adequately fit the data, as judged on statistical considerations. It is then necessary to choose one of the accepted models to provide the POD. One option is to select the model with the lowest AIC value from all statistically acceptable models. However, applying this approach may lead to models being excluded, which would otherwise provide higher, or lower, risk estimates. A second option is to select the model that leads to the highest extra risk or lowest BMDL on the basis that this selection is likely to be more conservative. This option is recommended by EFSA. A third option is to report a range of risk estimates from those models that provide an acceptable fit to the observed data. A fourth option is to average risk estimates/BMDLs based on the support for each model provided by the data (Wheeler and Bailer, 2007). It should be noted that this is not the simple averaging of the individual BMDL estimates, but a pooled analysis of the data. This model-average (MA) approach better characterises the uncertainty in the value of the BMDL that derives from ignorance of the true dose–response (Wheeler and Bailer, 2007), and hence is expected to be numerically higher than the lowest BMDL value resulting from applying a suite of models (Benford et al., 2010). EFSA (2009) indicated that this method is more advanced that the other options but needs to be fully developed and validated before they would recommend it.

14. Different software programs are currently available for BMD analysis. The US EPA developed the Benchmark Dose Software (BMDS). PROAST is another BMD software package, developed by the Dutch National Institute for Public Health and the Environment. Both these software package are suitable for dose-response analysis and deriving a BMDL from the dose-response data. The Dutch National Institute of Public Health and the Environment and EPA collaborate to achieve consistency between the BMDS and PROAST software. EFSA (2011) produced a technical report on the use of these two software packages for applying the BMD approach in risk assessment. Both are available free of charge.

The T25 approach

15. Although primarily used in carcinogenic potency estimates, the T25 approach can also be used to derive a POD. The T25 is defined as the dose eliciting a 25% increase in the incidence of a specific tumour above the background level within the standard lifespan of that species. ~~The T25 approach is a simple method for deriving a POD,~~ It was originally proposed by Dybing et al. (1997) and further developed by Sanner et al., (2001). The methodology does not require elaborate statistical methods. The T25 is determined by simple linear interpolation. According to Dybing et al. (1997) the data used for calculating a T25 should preferentially be from long term carcinogenicity bioassays. The estimation of T25 is dependent on the incidence of tumours at a selected site at a single dose level. The minimum data requirements to calculate a T25 are one incidence level significantly greater than the controls (Gillespie et al., 2011). The T25 is influenced by the quality of the bioassay information (e.g. design and evaluation of studies), and factors such as time to first tumour, the influence of toxicity on tumour induction and mortality and the approach taken regarding statistical analysis of tumour data. There may also be uncertainties regarding the application of the T25 for potency ranking particularly with regard to selection of the most sensitive site relevant for humans, the relevance of rodent tumours for humans and different cancer susceptibilities between rodent species (ECETOC, 2002). Using the T25 method, Sanner and Dybing (2005) found a good correlation between the values based on human epidemiological data and those based on animal experiments, although the data available for such comparison were limited. Previously, t~~T~~he T25 approach has been used in risk assessment for regulation of non-food, genotoxic carcinogenic chemicals in the EU (EFSA, 2006).

Comparing ~~T25 and~~ BMD and T25 methodology for use in risk assessment

16. T25 and the BMD methodology differ in that the T25 is calculated from one data point on the dose-response curve whereas the BMD is derived from dose response modelling of all available data on the dose response curve (EFSA, 2005).

17. Dybing et al. (2008) compared the ~~MOE~~margin of exposure (MOE), the numerical value obtained by dividing a point of departure on the dose response curve by estimated human exposure to the chemical ~~s~~ for 6 substances obtained using either the BMDL10 or the T25. They found that MOEs obtained using the T25 as the POD were on average around 2.35 times higher than those derived using the BMDL10 as the POD (Dybing et al., 2008). Benford et al. (2010) compared MOEs for 12 substances in food that are genotoxic and carcinogenic (5 of which were the same as those examined by Dybing et al., 2008) and found that the ratio of MOEs derived from a T25 value varied from those using a BMDL10 value by between 0.9 and 4.6, with a mean of 2.9 and a median of 2.6. These results were in line with the expected ratio of 2.5 to account for the 25% vs. 10% risk, assuming linearity in the dose-response, when comparing the T25 with the BMDL10 (Benford et al., 2010).

18. In the Committee's discussion of the MOE approach ~~Margin of Exposure approach (MOE)~~ for G06, the guidance document on Risk characterisation, the Committee considered the use of the BMDL10 as a point of departure superior to the T25.

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19. In the case where the dose response data are inadequate for deriving an estimate of the BMD10 or BMDL10, EFSA (2005) recommended the use of the T25 as a POD. However, use of this approach when it was not possible to derive a BMDL10 was questioned by Benford et al. (2010). As the BMD methodology uses all the available data, if a dataset does not allow derivation of a BMDL, even at a dose rate higher than 10%, e.g. a BMDL25, the dataset may not be suitable for derivation of a meaningful POD at all. An example would be if there is a very high incidence of tumours at all dose levels, in which case it would not be feasible to derive a BMDL, however, a T25 could be calculated by dividing the lowest dose level by the ratio of the percentage response to 25%. The resultant T25 value though would be meaningless. Therefore in the event that it is not possible to derive a BMDL10, the Committee does not recommend the routine use of the T25.

The TD50 Approach

20. The TD50 (Peto et al., 1984) is defined as the chronic dose-rate which would induce tumours in a given target site(s), in 50% of the test animals at the end of a standard lifespan for the species, provided that there were no tumours in control animals. However, since the tumour(s) of interest often do occur in control animals, the TD50 is more precisely defined as the daily dose rate required to halve the probability of remaining without tumours at the end of a standard life span. TD50 values have been estimated for chemicals listed in the Carcinogenic Potency Database developed by Gold and Zeigler (http://potency.berkeley.edu/cpdb.html) (Gold et al., 1984, 1997).

21. The TD50 concept is based on the assumption that there is linearity between dose and hazard until tumour onset, which may be complicated by premature deaths by causes other than tumour formation. The concept also depends on the assumption that tumour onset times are observable prior to mortality and as a result the approach relies heavily on careful observation of the animals. Tumours that are discovered after death may cause confounding between mortality and tumour onset and would ultimately result in a biased TD50 estimate. Alternatively, tumours that do not significantly alter survival and remain undiscovered until death would result in the TD50 value relating to the 'rate of death with tumour', rather than the tumour incidence rate. This undermines the objective of the carcinogenicity study, which is to evaluate tumour incidence. A description of the TD50 methodology and the complex statistical analysis involved in the derivation is provided at: http://toxnet.nlm.nih.gov/cpdb/td50.html.

The NOAEL (no-observed-adverse-effect-level) approach

23. For the majority of toxicological effects, with the exception of most genotoxicity, it is generally assumed that there is an exposure threshold below which no adverse effects occur. The NOAEL (no-observed-adverse-effect-level) approach was traditionally the method of choice for determining a point of departure for such effects, including carcinogenicity by a non-genotoxic mode of action. In human risk assessment, the NOAEL has been used to establish health based guidance values such as acceptable daily intakes (ADIs) for food additives and pesticide residues,

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and tolerable daily intakes (TDIs) and tolerable weekly intakes (TWIs) for contaminants. These guideline values are derived from the highest NOAEL for the most sensitive effect identified in human epidemiological studies or from subchronic or chronic studies in laboratory animals.

24. The highest administered dose at which no statistically significant difference from the concurrent control group is observed is designated the NO(A)EL, depending on whether the effect is considered adverse or not. To avoid unnecessarily conservative risk estimates, risk assessment is based on adverse effects rather than on minor or adaptive effects and hence the NOAEL is used as the POD. If a statistically significant effect is observed at all dose levels, the lowest dose used in the study, i.e. the LOAEL (lowest-observed-adverse-effect-level), may be used as the POD. Typically the NOAEL (or if one is not available, the corresponding LOAEL) is identified for the most sensitive relevant effect in the most sensitive species, with the adverse effect associated with the lowest NOAEL regarded as the critical effect of human relevance. The associated NOAEL is used as the POD. The NOAEL approach is easy to apply and as it has been the standard method for deriving PODs for a long time, it is familiar to most risk assessors (US EPA, 2000).

25. However, the NOAEL approach has a number of limitations. A major limitation is its constraint to be one of the experimental doses. The approach does not take into consideration dose spacing, the shape of the dose-response curve, the number of animals per group, or the statistical variation in the response and its measurement. The NOAEL approach tends to give lower health-based guidance values for studies with a higher power to detect adverse effects, which in effect “penalizes” better-designed studies (WHO, 2009). It should also be noted that studies with low power (e.g. small group sizes) and/or insensitive methods may only detect relatively large effects, resulting in higher NOAELs. This is in contrast to the BMDL, which “rewards” better-designed studies.

26. Despite the adoption of the BMD approach as an alternative to the NOAEL in determining a POD, there continues to be a need for the NOAEL/LOAEL approach. Not all data sets are amenable to BMD modelling such as those resulting from incomplete data availability or from a lack of models that can describe a data set adequately (US EPA, 2012) and the NOAEL approach can be used in this instance. A typical situation where the NOAEL approach is applicable whereas the BMD approach is not, is when there is a response only in the highest dose group.

Potency ranking of genotoxic carcinogens

27. Data from animal bioassays can be used to rank carcinogenic potency without reference to human intake. Carcinogenic potency estimates, as described in paragraph 3, make use of the available dose response data and points of departure can be derived from TD50, T25 or BMD approaches for use in potency ranking. For example in a series of publications Gold et al. tabulated data on a large number of compounds allowing their carcinogenic potency to be expressed as the TD50 (Gold et al., 1997). These values can be used to indicate the relative potency of a series of compounds.

28. Relative potency estimates could have some pragmatic use in carcinogenic risk assessment as an aid in the prioritisation of genotoxic carcinogenic substances, but are not considered adequate for quantifying cancer risks. The uncertainties inherent in potency ranking mean that relative potencies should not be over-interpreted. For example, it is unclear whether the relative ranking identified in the observed dose range would be maintained at low doses, and whether the relative potency in animal studies would be applicable to humans. Potency Equivalence Factors (PEFs) have been suggested in circumstances where there is a good surrogate compound for comparison, e.g. inhalation of PAH's (Collins, 1998; Pufulete et al., 2004). Pufulete et al. (2004) suggested that an approach based on PEFs could be developed to include highly potent PAHs provided an appropriate reference data set for relevant PAHs using a route acceptable for inhalation risk assessment is selected. The US EPA (2010b) also developed an approach to assessing cancer risk for polycyclic aromatic hydrocarbon (PAH) mixtures using relative potency factors (RPFs), which estimates the cancer risk of individual PAHs relative to that of benzo[a]pyrene (BaP). The US EPA suggest that their RPFs are applicable to all routes of exposure, but acknowledge that there is appreciable uncertainty in doing this. The COC notes that PHE have adopted a surrogate marker approach rather than the use of PEFs for assessment of PAHs from contaminated land (HPA, 2010). Otherwise, to date, there has been little use of Potency Equivalence Factors for carcinogenicity.

29. Comparing the TD50 and T25 approaches for estimating potency, the TD50 has an advantage in that it accounts of effects of chemicals on survival, but requires specific software to undertake its derivation. In contrast, the T25 is quick and easy to calculate. There is evidence of a good correlation between rank order produced by TD50 and T25 (Dybing, 1997). In 2005, the COC compared the TD50 with the T25 (http://www.iacoc.org.uk/papers/documents/cc0619.pdf) in an attempt to develop an approach for potency ranking of genotoxic carcinogens for single exposure. Very limited data were available for this purpose and little correlation was found for those substances for which it was possible to obtain TD50 and T25 values.

30. The Committee acknowledges that the T25 approach can be used in potency ranking of genotoxic carcinogens, but is of the view that the parameter should not be over interpreted. The reasons for this are that there are a number of basic uncertainties, such as whether the relative ranking identified in the observed dose range would be maintained at low doses, and whether the relative potency in animal studies would be applicable to humans. Currently, there is no need to use the T25 to rank non-genotoxic carcinogens, for which tolerable exposure levels can be derived using an approach based on knowledge of mode of action, identification of no observed adverse effect level, and use of uncertainty factors.

<u>Threshold of Toxicological Concern (TTC)</u>

31. The use of *de minimis* exposure values as a means of identifying substances of low concern was first proposed by Frawley (1967). This was further developed by the US Food and Drug Administration (FDA) (Rulis, 1986, 1989, 1992) for application to substances that do not contain a structural alert for genotoxicity/ carcinogenicity, but intended to protect against all types of toxicity including

carcinogenicity. Analysis of the 500 carcinogens then in the Cancer Potency Database (CPDB), based on virtually safe doses (for a 1 in 10^6 excess cancer risk) derived from the TD50s, led to the adoption by the FDA (1995) of a Threshold of Regulation of 0.5 µg/kg of diet (equivalent to 1.5 µg/day) for substances used in food contact materials, for which consumers would be protected "with reasonable certainty of no harm", even if that substance was later shown to be a carcinogen. Cheeseman et al. (1999) later analysed and validated the approach using the expanded CPDB containing information on 700 chemicals (Gold et al., 1997). Cheeseman et al. (1999) identified certain categories of potent carcinogens which would not be covered by the Threshold of Regulation of 0.5 µg/kg of diet. These were azoxy compounds, benzidines, N-nitrosamines and aflatoxin-like compounds. A number of other groups were excluded, but these were not genotoxic and potency was estimated using linear extrapolation from the TD50, which would result in an appreciable overstimate. With the exclusion of these structural classes, it was considered unlikely that an unstudied compound would be both carcinogenic and have a potency far greater than the typical potency of studied compounds.

32. Subsequently, Kroes et al. (2004) re-evaluated the distribution of VSDs for carcinogens, grouped into structural classes, e.g. aromatic amines, benzidines. They concluded that, with a few exceptions, adequate protection would be provided (i.e. there was low probability that the risk from an untested chemical would be > 1 in 10^6) even from compounds that were genotoxic or carcinogenic using a TTC value of 0.15 µg/person/day. Groups of compounds that would not be covered by this value were aflatoxin-like-, azoxy- and N-nitroso-compounds, as well as steroids and dioxins, because of their very high potency, thus largely confirming the conclusions of Cheeseman et al. (1999). In their recent opinion, the EU DG SANCO committees added benzidines and hydrazines to this list.

33. When considered by the COC for the 2004 version of the guidelines, the application of the TTC to carcinogens was a relatively new approach and the Committee felt that "*careful consideration was needed of the biological, analytical and mathematical issues as well as a much wider database for validation. The Committee consider that it should not currently be used as a generic approach, as the proposed exclusions covered some important classes of genotoxic carcinogens (such as aflatoxin-like compounds, azoxy compounds and N-nitroso compounds) and a number of classes of other carcinogens, such as heavy metals and TCDD (Kroes* et al., *2004). However, as it is based on ranking by theoretical risk and exposure the Committee agree that it could be used, along with hazard identification and characterisation data, for prioritisation of chemicals, particularly for chemicals that are not subject to regulatory approval schemes."* Since 2004, experience on the application of the TTC approach has increased, and the approach itself has been refined, including proposals for use both for inhalation (Carthew et al., 2009; Escher et al., 2010) and dermal (Safford et al., 2008; Safford et al., 2011) exposure. The TTC approach has recently been reviewed by EU committees (EFSA and DG SANCO). A paper describing the development of the TTC concept since its introduction in 1995 and the respective EU committee opinions was recently presented at COC (http://www.iacoc.org.uk/papers/documents/CC2012-18TTCpaper.pdf).

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34. In their analysis, Munro et al. (1996) utilised a dataset comprising repeat dose oral toxicity data for 613 organic chemicals with 2941 associated NOEL values derived from a variety of non-cancer endpoints from sub-chronic, chronic, reproductive and developmental toxicity studies carried out in rodents and rabbits. NOELs for sub-chronic studies were adjusted to chronic exposure using a factor of 3. The 5th percentiles of the NOELs, grouped according to their respective Cramer et al. (1978) class (i.e. Class 1, 2 or 3), were used to derive TTC values by multiplying by 60 (assuming an average individual weighs 60 kg) and then dividing by a safety factor of 100, mirroring the ADI approach. This resulted in TTC values of 1800 µg/person/day (30 µg/kg bw per day) for Class 1 chemicals, 540 µg/person/day (9 µg/kg bw per day) for Class 2 chemicals and 90 µg/person/day (1.5 µg/kg bw per day) for Class 3 chemicals, respectively. EFSA has recommended that the TTC values should be expressed per kg body weight, so that they are applicable to different age groups, differing in body weight. It is considered that at oral lifetime exposures below the respective TTC value there is a low probability of any risk, even for a chemical with little or no toxicological data. The Joint Research Centre have developed a free software package, ToxTree, to enable Cramer classification of a chemical (http://toxtree.sourceforge.net/ and http://ihcp.jrc.ec.europa.eu/our_labs/predictive_toxicology/qsar_tools/toxtree).

TTC decision Tree

35. Kroes et al. (2004) combined considerations of structural alerts for genotoxicity with the approach developed by Munro et al. (1996) for *de minimis* exposure values for non-cancer endpoints, based on the structural classification scheme of Cramer et al. (1998) to develop a decision tree for application of the TTC approach to chemicals in food. This scheme was recently updated by EFSA (figure 1). First, compounds to which the TTC approach is not currently applicable are excluded. These are the groups of potent genotoxic carcinogens discussed above (the cohort of concern), metals, metal-containing compounds, other inorganic compounds, substances known or predicted to bioaccumulate, including polyhalogenated dibenzodioxins, dibenzofurans and biphenyls, proteins, substances with a steroid structure, insoluble nanomaterials, radioactive substances, mixtures of substances of unknown structure, substances acting locally and chemicals displaying pharmacological effects for which no readily accessible database is available.

36. The potential for genotoxicity of the compound is then determined, using predictive software, such as DEREK and ToxBoxes. A number of approaches are used by these packages to predict genotoxic potential, such as the scheme for structural alerts developed by Ashby and Tennant (1991). If there is no alert for genotoxicity, the chemical is assessed according to its Cramer classification, with the addition of an additional class for organophosphates.The resultant output is either that the compound in question is unlikely to represent a safety concern, or that chemical-specific toxicological data are required to carry out a risk assessment (Kroes et al., 2004; EFSA, 2012).

37. In 2009, Felter et al. proposed further refinements to the TTC decision tree, including consideration for chemicals that have structural alerts for genotoxicity but negative data from genotoxicity tests. They proposed using a higher threshold value of 1.5 µg/person/day as an appropriate TTC exposure limit in such cases. This was

based on the work by Cheeseman et al. (1999) on carcinogenic potency and results from Ames tests. This paper also suggested that, in circumstances where exposures were unlikely to be over a lifetime, a value of 1.5 µg/person/day may be appropriate for exposures which will not be longer than 1 year (Felter et al., 2009). The concept of a staged TTC was proposed by Mueller et al. (2006) and takes into account the fact that duration of exposure is a key factor impacting on the probability of a carcinogenic response. In 2010, the European Medicines Agency (EMA) agreed to the use of a staged TTC approach during clinical development of medicines for a less than lifetime exposure and recommended limits for daily intake of genotoxic impurities (GTIs) of 1.5, 5, 10, 20 and 60 µg/day for greater than 12-months, 6-12-months, 3-6-months, 1-3-months and less than 1-month, respectively. For single doses, an intake of 120 µg/day was agreed to be acceptable. (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002907.pdf).

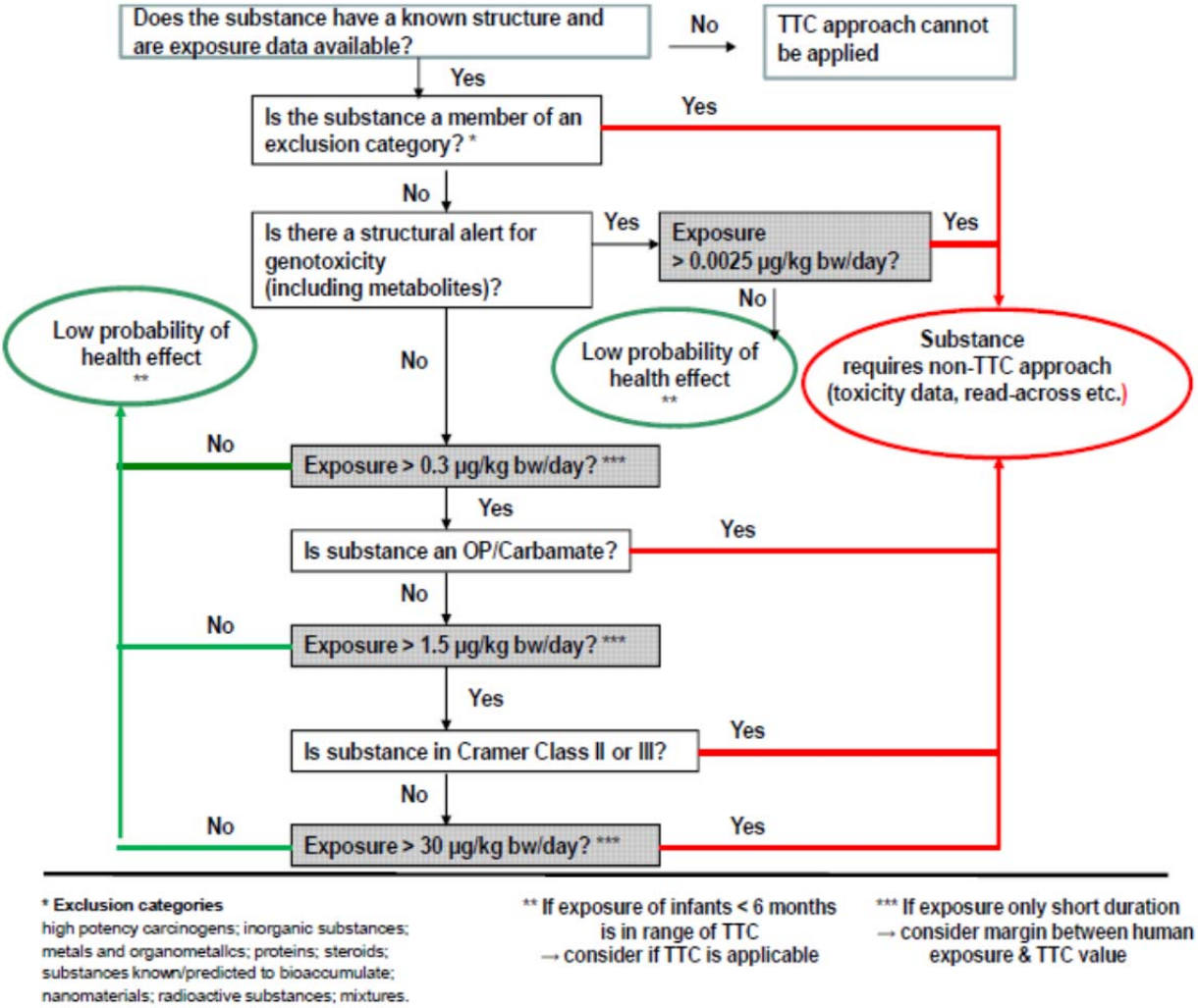

Figure 2: *The TTC decision tree suggested by EFSA* (2012)**.**

38. TTC values derived from the Cramer et al. classes are used by EFSA and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for flavouring substances. A TTC of 1.5 µg/day is used for different reasons as part of a staged assessment for the acceptability of known genotoxic impurities present in

pharmaceuticals (EMEA , 2006). This value (1.5 µg/day) is considered appropriate under such circumstances, as a risk of 1 in 10^5 (assuming linear extrapolation) is considered acceptable for human medicines. The use of a TTC of 1.5 µg/day by the EMA applies even to compounds that show evidence of genotoxicity in *in vitro* tests. A similar approach is used for genotoxic constituents of herbal medicinal products/preparations (EMEA, 2008).

39. The use of the TTC approach, covering both potential genotoxic and non-genotoxic endpoints, has been proposed for the assessment of metabolites and degradates of pesticide active substances (EFSA, 2012a). The TTC approach has also been proposed for household and personal care products (Blackburn et al., 2005), for skin sensitising substances (Safford, 2008) and for industrial chemicals assessed under REACH (ECHA, 2008).

TTC Endorsement by sister Committees

40. The COM published a statement in April 2012 on the genotoxicity testing and hazard assessment of impurities. As part of this, Members agreed that the TTC was a useful concept in identifying impurities requiring genotoxicity assessment, although reference needed to be made to the excluded classes of most concern, e.g. aflatoxin-like, azoxy and N-nitroso compounds which are potent genotoxic carcinogens.

41. ~~Overall view of COC on TTC to be inserted here~~. The COC endorse the views of its sister committee COM and the views of EFSA and the DG SANCO Committees on TTC.

New fields and Developments in deriving Points of Departure

42. Sand et al. (2011) developed a new approach for derivation of a POD based on the concept of a signal-to-noise crossover dose (SNCD) and compared it with other methods for deriving the POD. The SNCD provides an estimate of the lowest dose that can be derived as a POD for risk assessment without low-dose extrapolation. It is defined as the dose at which the additional risk equals the “background noise” or a specified fraction thereof. Background noise is defined as the difference between the upper and lower bounds of the two-sided 90% confidence interval (CI) on absolute risk. Sand et al. (2011) concluded their comparison of the different methods by noting that if the standard BMD approach is used then the BMDL10 is the most appropriate POD and that the SNCD should be developed further. Responding to the new SNCD approach, Chiu et al. (2012) proposed augmenting the statistical approach for human risk assessment by additional steps so that inter- and intra-species differences and other biological considerations relating to the key end points are addressed.

43. The SNCD approach gives equivalence with the BMDL10 approach using a default uncertainty factor of 100. The SNCD-based exposure guideline was derived by linear extrapolation from the upper bound on extra risk at the SNCD (UERSNCD) down to a target risk of 1/1,000. However, it should be noted that for a genotoxic carcinogen, it is likely that target risk values would be appreciably lower

than this (typically 1 in 10^5 or 1 in 10^6). The Committee will continue to keep a watching brief on the developments of the SNCD approach as an alternative approach to deriving a POD.

~~Sand et al~~et al~~. (2011) developed a new approach for derivation of a POD based on the concept of a signal-to-noise crossover dose (SNCD). The SNCD provides an estimate of the lowest dose that can be derived as a POD for risk assessment without low-dose extrapolation. It is defined as the dose at which the additional risk equals the "background noise" or a specified fraction thereof. Background noise is defined as the difference between the upper and lower bounds of the two-sided 90% confidence interval (CI) on absolute risk. Considering this new approach of SNCD, Chiu et al~~et al~~. (2012) proposed that for human risk assessment an increase in statistical approaches is required so that interspecies and intraspecies adjustments and biological considerations relating to the key end points are addressed.~~

Overall Summary

44. The Committee recommend the use of the BMDL as the POD for all carcinogens. For genotoxic carcinogens, the likeliest use of the BMDL would be in calculating an MOE as outlined in Guidance Statement G06. For non-genotoxic carcinogens, the BMDL can be used to establish Tolerable Daily Intakes/ Acceptable Daily Intakes (TDI/ADI) using uncertainty factors, if carcinogenicity is the critical endpoint. If a BMDL cannot be set for a chemical, the Committee agree that although it might be possible to derive a T25 for the dataset, it is not recommended.

45. The Committee is of the view that potency estimates can be of pragmatic use in carcinogenic risk assessment as an aid to prioritising carcinogenic substances (e.g. for risk re-evaluation), but consider that such potency estimates do not provide a quantitative estimate of risk. Although potency estimates can be used to rank chemicals within a particular group (such as structurally related groups of putative genotoxic chemicals), extrapolating from high to low dose and from animals to humans introduce sources of uncertainty.

46. The Committee acknowledged that it was well recognised that the TTC approach provides a pragmatic means of ~~prioritising~~ assessing potential genotoxic carcinogens~~ for further assessment~~. Excluding specific groups of potent genotoxic carcinogens, where a compound possesses a structural alert for genotoxicity a TTC value of 0.15 µg/person/day (0.0025 µg/kg bw per day) provides a conservative exposure level below which there is a low probability of any risk. However, the Committee reiterated that the TTC was not a replacement for data for any chemical under consideration, but could be used where data are lacking or insufficient, to help in reaching an informed decision based on weight of evidence.

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COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

COC Guidance Statement G05: Glossary

Acceptable daily intake (ADI): estimate of the amount of a substance in food or drink, expressed on a body weight basis (e.g. mg/kg bodyweight), that can be ingested daily over a lifetime by humans without appreciable health risk.

Benchmark dose (BMD): a point of departure (qv) in a carcinogenicity bioassay at which there is a specified cancer incidence above the level in the control group.

BMDL: the lower 95% confidence limit of the benchmark dose.

$BMDL_{10}$: lower 95% confidence limit of the benchmark dose for a 10% response.

Benchmark Response (BMR): An adverse effect, used to define a benchmark dose (BMD). The change in response rate over background of the BMR is usually in the range of 5-10%, which is the limit of responses typically observed in well-conducted animal experiments

Dose-response relationship: the change in effect caused by differing doses of a chemical after a certain exposure time.

Margin of Exposure (MOE): the numerical value obtained by dividing a point of departure on the dose response curve by estimated human exposure to the chemical.

No Observed Adverse Effect Level (NOAEL): The highest administered dose at which no adverse effect has been observed.

Point of departure (POD): a defined level of effect that can be determined from dose response data from a study, such as the dose level associated with a tumour incidence which is 10% above the incidence in the control group.

Reference dose (RfD): an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Reference concentration (RfC): When assessing inhalation exposure, “reference concentrations" (RfCs) are used instead of RfDs

Signal to Noise Crossover Dose (SNCD): provides an estimate of the lowest dose that can be derived as a POD for risk assessment without low-dose extrapolation. It is defined as the dose at which the additional risk equals the “background noise” or a specified fraction thereof. Background noise is defined as the difference between the upper and lower bounds of the two-sided 90% confidence interval (CI) on absolute risk.

T25: the dose eliciting a 25% increase in the incidence of a specific tumour above the background level.

TD_{50}: the daily dose required to halve the probability of remaining without tumours at the end of a standard life span.

Threshold of Toxicological Concern (TTC): a concept that refers to the establishment of a level of exposure for all chemicals, whether or not there are chemical-specific toxicity data, below which there would be no appreciable risk to human health.

Tolerable daily intake (TDI): estimate of the amount of a contaminant, expressed on a body weight basis (e.g. mg/kg bodyweight), that can be ingested daily over a lifetime by humans without appreciable health risk