CC/2017/22

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

Updated Guidance Statement G05: Defining a Point of Departure and Potency Estimates in Carcinogenic Dose Response – second draft

The Committee has previously agreed to regularly review the published COC guidance statements to ensure they remain up to date. As part of this process G05 on points of departure and potency estimates has been updated and was discussed as a first draft in July 2017.

At the meeting it was agreed that an interim update should be made to the document but a preamble section added to highlight that a full revision would be undertaken following consideration of the benchmark dose approach (CC/2017/20) and the threshold of toxicological concern (CC/2017/21) which are also presented at this meeting. Other comments made in July 2017 for consideration in a full revision to the document included considering the order of presentation of the different types of points of departure and potency estimates, and linking to other work in the area such as the COM work on quantitative risk assessment that references the benchmark dose approach and is expected to be published in towards the end of the year.

Annex A to this paper contains the second draft updated document in tracked changes with the amendments compared to the original version 1.0.

Members are invited to indicate whether they are content to publish this version subject to any minor amendments from the meeting as an interim update, to be followed by a fuller revision in early 2018.

Secretariat
November 2017

CC/2017/22 Annex A

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Second draft of updated document in tracked changes with the amendments compared to the original version 1.0.

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Committee on CARCINOGENICITY

COC/G05 – Second draft Version 1.01 (20147)

Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

Defining a Point of Departure and Potency Estimates in Carcinogenic Dose Response

Preamble to 2017 update: In 2017, this document has been given an interim update, but a full revision will be required as there are a number of new developments in the field, e.g. updated guidance from the European Food Safety Authority (EFSA) on benchmark dose modelling, and joint work by EFSA and the World Health Organisation (WHO) on the threshold of toxicological concern. Brief aspects of these have been incorporate in the text here, though the Committee will be formally reviewing the new guidance and other relevant papers before a fully revised version is published.

1.0 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) such as the Benchmark Dose (BMD) and potency estimates**,** such as the T25 and TD50, and describes how they can be used to estimate the relative potency of carcinogens. However, the BMDL[3] is the most widely preferred POD approach and the COC recommends its use. Similarly, in recent times, the BMDL is the preferred POD for thresholded 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 the term **‘“**NOAEL**”’** in such cases does not necessarily imply the existence of a threshold in the dose-response relationship. This guidance document also details the Threshold of Toxicological Concern (TTC) approach which can help to identify priorities for more detailed carcinogenicity evaluation, particularly for chemicals not subject to regulatory approval schemes.

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 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 environmental concentrations are usually much lower than those used in animal studies and often also lower than those to which individuals have been exposed in studies used to characterise effects in humans (e.g. observational epidemiological studies). **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

1 This G02 guidance has yet to be published**,** at time of the latest **publication** update of G05, 2017**4**
2 This G03 guidance has yet to be published, at time of publication of G05, 2014
3 BMDL: Lower 95% confidence limit of the benchmark dose for a specific level of response (usually 10%)

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 is often used as a surrogate. A POD is defined as the dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence of a tumour or a change in response level from a dose-response model (BMD), or a NOAEL or LOAEL for an observed incidence, or change in level of response **(US EPA IRIS)**. 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.

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 POD 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).

2.0 Points of Departure and Potency Estimates

2.1 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 or tolerable daily intakes (ADIs or TDIs) for effects for which it is assumed there is a threshold. It was subsequently developed further within the US EPA (US EPA, 1995). Both the European Food Safety Authority (EFSA) and the World Health Organization (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. This includes carcinogenicity by a genotoxic mode of action. The BMD approach has a number of advantages over the NOAEL approach. 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 enables quantification of the uncertainties in the dose-response data using statistical methodology (EFSA, 2009, 2017). Although the current international guidelines for study design have been developed with the NOAEL approach in mind, they offer no obstacle to the application of the BMD approach. The current guidelines may, however, not be optimal given that the BMD approach allows for more freedom in balancing between number of dose groups and group sizes (Slob, 2014). As these guidelines are revised, e.g. within the OECD Test Guidelines Programme, the possibility to recommend study designs that tend to result in better dose–response information (e.g. more dose levels with the same total number of animals) should be taken into account.**However, it should be noted that most studies are optimised in their design to identify the NOAEL**.

7. The BMD_{xx} 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 fitting a mathematical curve to the dose-response data over the range of observable responses from animal studies or human studies (if available), using a selection of different models. From each statistically acceptable modelled dose–response curve, **a** values for the BMD and the lower and upper bound 95% confidence limits (BMDL and BMDU) are obtained (see paragraphs 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 ($BMDL_x$) 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, 2017). Dichotomous (quantal or incidence) data describe whether an effect has occurred in an individual or not, e.g.**,** presence of tumour, death. The tumour 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 animal dose-response data due to the presence of confounders and imprecision in the exposure estimates (EFSA, 2009, 2017). 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 for effects such as DNA damage an approach appropriate for continuous data would need to be used.

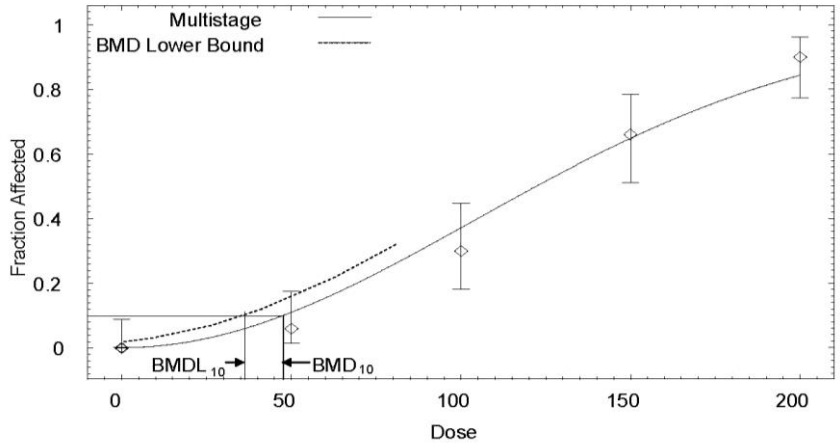

Figure 1. Example of a model fit to dichotomous data, with BMD and BMDL indicated. The fraction of animals affected in each group is indicated by diamonds, and the error bars indicate 95% confidence intervals for the fraction affected. The BMR in this example is an extra risk of 10% (or 0.1 fraction responding). The fitted model is shown by the solid curve, and the BMD corresponding to 10% extra risk on this curve is notated BMD_{10}. The lower bound on BMD10, notated $BMDL_{10}$, 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).

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, 2017). 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 dataset is suitable for modelling. In the 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 specification of the BMR, model selection of candidate dose-response model(s), model fitting/ assessmentaveraging/calculation of BMD confidence interval and BMDL, and data reporting.**

10. In preparation for BMD modelling, the BMR must also be chosen. For quantal responses, the BMR is expressed in terms of a percent increase in risk[4] of adverse

4 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.

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, 2017) 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, 2017).

11. Both the WHO/IPCS and EFSA have produced guidance on dose–response modelling, including guidance on cancer dose-response data (**WHO/**IPCS, **(**2009b**)** and EFSA, 2009, 2017). Table 1 lists the models for BMD analysis for quantal data recommended by EFSA (2017). It should be noted that the models outlined in the t**T**able 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, 2017) 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).

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 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. The EFSA guidance (2009) 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 the l**L**ikelihood-ratio test and EFSA (2009) recommended**s** a minimum goodness of fit value of p = 0.05 for model acceptance based on log-likelihood. For dichotomous data, the US EPA software employs Pearson's chi-squared goodness of fit test (US EPA, 1995). The US EPA (2012) recommends a minimum goodness of fit p value of p = 0.1 for model acceptance. The 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 Pearson's chi-squared goodness of fit test can also be used for selection within a nested series. The latest EFSA guidance recommends that the AIC should be used (instead of log-likelihood) to characterise goodness of fit (EFSA, 2017)**.. 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 (2009) has 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.

Table 1: Recommended quantal mModels for use in the BMD approach [(1)] (taken from EFSA guidance, 201709)

Model	Number of model parameters	Model expression mean response (*y*) as function of dose (*x*)	Constraints
Quantal data [(2)]			
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 ≤ *a* ≤ 1, b>0, c>1
Log-probit	3	y = a + (1-a) CumNorm(log(x/b)/c)	0 ≤ *a* ≤ 1, b>0, c>0
Weibull	3	y = a + (1-a) exp($(x/b)^c$)	0 ≤ *a* ≤ 1, b>0, c>1
Gamma	3	y = a + (1-a) CumGam(bx^c)	0 ≤ *a* ≤ 1, b>0, c>1
Linearized multistage (LMS) family [(3)]			
Two-Stage	3	y = a + (1-a) exp(– bx – cx^2)	a>0, b>0, c>0
Latent variable models **(LMVs)** based on continuous models (1)**Three-Stage**	Depends on underlying continuous model**4**	These models assume an underlying continuous response, which is dichotomised into yes/no response based on a (latent) cut-off value that is estimated from the data **y = a + (1-a) exp(– bx – cx^2 – dx^3)**	As for continuous models (2)**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) In epidemiology, additional models, e.g. y=a+bx, are also used
2) For the constraints given here, the models result in increasing dose-response curves (1) The latent variable models are implemented in PROAST.
(2) See EFSA (2017)**3) 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 model, e.g. 2 for a two-stage model.**

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 then 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 wais recommended by EFSA (2009). 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 ('Model Averaging') (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). Revised EFSA guidance now recommends Model Averaging as the preferred approach, combining results from each of the fitted models to establish a final BMD confidence interval. However, selection/rejection of models can be considered as a sub-optimal alternative in situations where Model Averaging tools are not available (EFSA, 2017) **EFSA (2009) indicated that this method is more advanced than the other options but needs to be fully developed and validated before they would recommend it.**

Comment [K1]: There is more detailed consideration of changes in section 5 of the EFSA 2017 revised guidance.
This includes a flow chart to establish the BMD confidence interval and BMDL.

More detail on this can be added in the full revision to the document

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, and the basis on which EFSA now provide a web-based platform for performing BMD analysis. Both these software packages 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 software packages are available free of charge.**

15. Once the BMDL is derived as the POD, the risk assessor moves to the risk characterisation stage of the risk assessment which brings together the hazard identification and hazard characterisation stages and the exposure assessment process (see Risk Characterisation Guidance Statement G06).

2.2 The T25 approach

16. Although primarily used in carcinogenic potency estimates, the T25 approach can also be used to derive a POD. For example, although the European Chemicals Agency (ECHA) prefers $BMDL_x$ as a starting point, if the data do not permit B**D**MD analysis, ECHA suggests that the T25 can be used. 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. 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 or, in some cases, extrapolation beyond the data points. 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. The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) has evaluated the use of T25 estimates for regulatory risk assessment of non-threshold carcinogens (ECETOC, 2002). 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). The T25 is also the method used by the EU to assess relative potency for the setting of specific concentration limits of preparations and mixtures (EC, 1999). 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, the T25 approach has been used in risk assessment for regulation of non-food, genotoxic carcinogenic chemicals in the EU (EFSA, 20056).

2.3 Comparing BMD and T25 methodology for use in risk assessment

17. 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).

18. Dybing et al. (2008) compared the Margin of Exposure (MOE), the numerical value obtained by dividing a POD on the dose- response curve by estimated human exposure to the chemical, for 6 substances obtained using either the $BMDL_{10}$ 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 $BMDL_{10}$ 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 $BMDL_{10}$ 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 relationship, when comparing the T25 with the $BMDL_{10}$ (Benford et al., 2010).

19. In the Committee's discussion of the MOE approach for G06, the guidance document on Risk Characterisation, the Committee considered the use of the BMD approach as a means of deriving a POD to be superior to that of the T25.

20. In the case where the dose- response data are inadequate for deriving an estimate of the BMD_{10} or $BMDL_{10}$, EFSA (2005) recommended the use of the T25 as a means of deriving a POD. However, use of this approach when it was not possible to derive a $BMDL_{10}$ 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 $BMDL_{25}$, 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**but**,** a T25 could still be calculated by dividing the lowest dose level by the ratio of the percentage response to 25%. However, the resultant T25 value would be meaningless. The Committee agrees with this view and, therefore, in the event that it is not possible to derive a $BMDL_{10}$, the Committee does not recommend the routine use of the T25.

2.4 The TD50 approach

21. 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 (CPDB) developed by Gold and Zeigler (https://toxnet.nlm.nih.gov/cpdb/cpdb.html, accessed 09/05/17**http://potency.berkeley.edu/cpdb.html**) (Gold et al., 1984, 1997).

22. 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 from 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 within the study period 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 (accessed 09/05/17).

23. The Committee reiteratesd its previous position that the TD50 is a practical quantitative estimate of carcinogenic potency for the ranking of genotoxic carcinogens.

2.5 The NOAEL (No Observe Adverse Effect Level) approach

24. For the majority of toxicological effects, with the exception of most genotoxic effects or where extensive testing has failed to identify a threshold (e.g. lead), 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, and tolerable daily intakes (TDIs) or tolerable weekly intakes (TWIs) for contaminants. These **guideline** health-based guidance values are derived from the highest NOAEL for the most sensitive effect identified in human epidemiological studies or from sub-chronic or chronic studies in laboratory animals.

25. The highest administered dose at which no statistically significant adverse difference from the concurrent control group is observed is designated the NOAEL. 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 adverse 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 has been the standard method for deriving PODs for a long time and it is familiar to most risk assessors (US EPA, 2000).

26. However, the NOAEL approach has a number of limitations. A major limitation is theits constraint for the NOAEL 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 (WHOIPCS, 2009a). 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.

27. 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 dataset 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.

3.0 Potency Ranking of Genotoxic Carcinogens

28. 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 potencies**y** to be expressed as the TD50 (Gold et al., 1997). These values can be used to indicate the relative potencies**y** of a series of compounds.

29. 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 polycyclic aromatic hydrocarbons (PAHs) (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 (2010**b**) also developed an approach to assessing cancer risk for 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 suggests that their RPFs are applicable to all routes of exposure, but acknowledges that there is appreciable uncertainty in doing this. The COC notes that PHE has adopted a surrogate marker approach rather than the use of PEFs for assessment of the public health risk of PAHs in contaminated land (HPA, 2010). Otherwise, to date, there has been little use of P**otency** E**quivalence** F**actor**s for carcinogenicity.

30. Comparing the TD50 and T25 approaches for estimating potency, the TD50 has an advantage in that it takes account of effects of chemicals on survival, however **but that** it 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 200**5**6, 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 among those substances for which it was possible to obtain chronic TD50 and T25 values, compared to acute T25 values (COC, 2006).

31. The Committee acknowledges that the T25 approach can be used in potency ranking of genotoxic carcinogens, but is of the view that the statistics should not be over-interpreted. The reason**s** for this is**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 a **no observed adverse effect level**NOAEL, and the use of uncertainty factors.

4.0 The Threshold of Toxicological Concern (TTC)

4.1 Development of the TTC

32. 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. 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 an intake of 1.5 µg/person/day) for substances used in food contact materials. At this level, it was intended that 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 overestimate. 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.

33. Subsequently, Kroes et al. (2004) re-evaluated the distribution of virtual safe doses (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 potenciesy, 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.

34. 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 concluded 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."* (COC, 2004).

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, Tluczkiewicz et al., 2016) and dermal (Safford et al., 2008; Safford et al., 2011; Safford et al., 2015; Roberts et al., 2015) exposure. The TTC approach has recently been reviewed by EU committees (DG SANCO, 2012; EFSA, 2012b; EFSA/WHO, 2016 **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 in 2012 (Paper CC/2012/18, available from: http://webarchive.nationalarchives.gov.uk/20140506122048/http://www.iacoc.org.uk/papers/index.htm**http://www.iacoc.org.uk/papers/documents/CC2012-18TTCpaper.pdf**).

35. 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 EU Joint Research Centre has developed a free software package, ToxTree, to enable Cramer classification of a chemical (http://toxtree.sourceforge.net/ **and**).

4.2 TTC decision tree

36. 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. (1978) to develop a decision tree for application of the TTC approach to chemicals in food. This scheme proposed by **was recently updated by** EFSA in 2012 is shown in **(F**figure 1, but the Committee notes there is a revised scheme recommended by EFSA and WHO (2016) which will be considered in the full revision to this document**)**. 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.

37. 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, 2012b).

38. 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 M**üue**ller 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. (EMA, 2010).

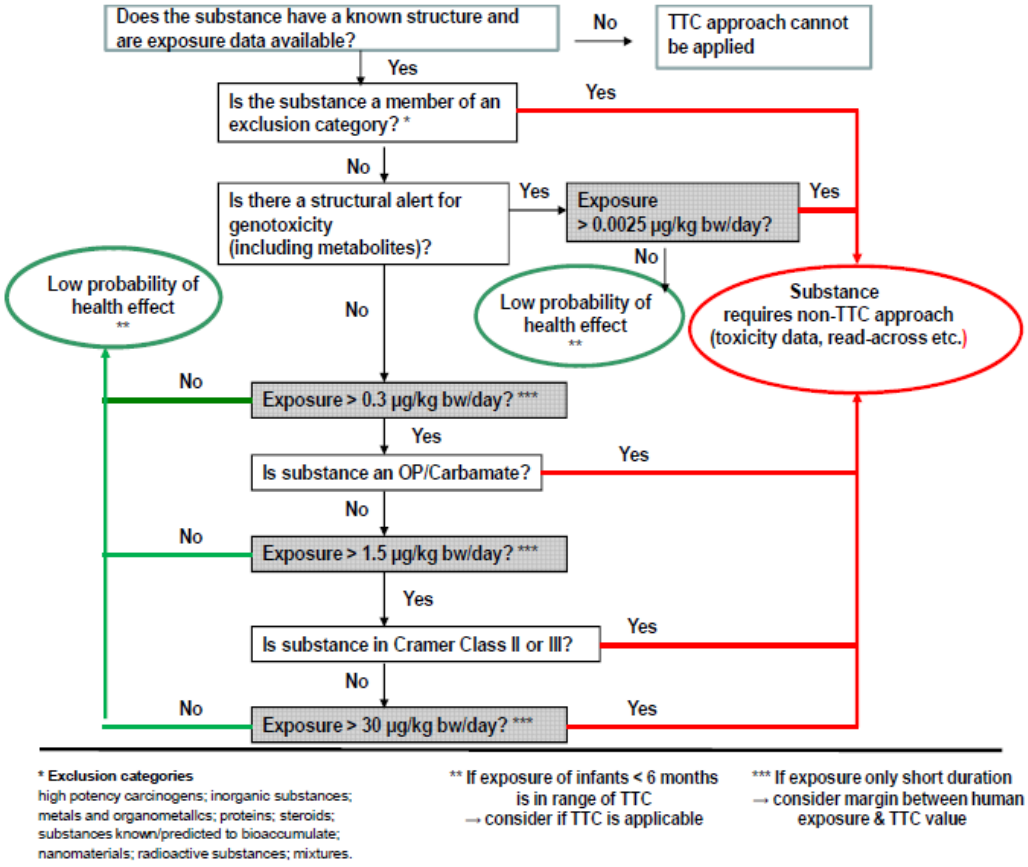

Figure 2: *The TTC decision tree suggested by EFSA* (2012b).

Comment [BG2]: Use of EFSA and WHO 2016 to be considered for full update

39. 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 EMEA 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).

40. 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).

4.3 TTC endorsement by sister committees

41. 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 (COM, 2012).

42. The COC endorses the views of the COM and the views of EFSA and the DG SANCO Committees on the TTC.

Comment [BG3]: Check on full update whether to also include WHO

5.0 New fields and Developments in Deriving Points of Departure

5.1 The Signal-to-Noise Crossover Dose (SNCD) approach

43. 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 $BMDL_{10}$ 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.

44. The SNCD approach gives equivalence with the $BMDL_{10}$ 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 in 10^3. 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 but notes that there have been no further publications on this methodology since 2011.

Comment [K4]: To update.

Environ Health Perspect. 2017 Apr;125(4):623-633.
Comparison of Points of Departure for Health Risk Assessment Based on High-Throughput Screening Data.
Sand S[1], Parham F, Portier CJ, Tice RR, Krewski D.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5381992/

From the abstract:
"Objectives:
The aim of this study was to compare different PODs for HTS data. Specifically, benchmark doses (BMDs) were compared to the signal-to-noise crossover dose (SNCD), which has been suggested as the lowest dose applicable as a POD."

Does the Committee wish to review this paper/ update its opinion on the SNCD approach?

6.0 Summary

45. The Committee recommends the use of the BMDL as the POD for all carcinogens. For genotoxic carcinogens, the likeliest use of the BMDL would be to calculate a MOE as outlined in Guidance Statement G06. For non-genotoxic carcinogens, the BMDL can be used to establish guideline values such as 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 agrees that, although it might be possible to derive a T25 from the dataset, this**it** is not recommended.

46. 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 considers 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 introduces sources of uncertainty.

47. The Committee recognises that the TTC approach provides a pragmatic means of assessing whether exposure to a chemical is of low concern or whether further testing is required. However, the Committee reiterates that the TTC is not a replacement for data on any chemical under consideration, but could be used where data are lacking or insufficient, to help in reaching an informed decision.

COC
July 2014 (updated 2017)

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Comment [K5]: (this document is no longer available)

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