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CC/07/14

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

**FURTHER CONSIDERATION OF THE MOE APPROACH**

The HPA is exploring whether the MOE approach could be applied to the management of the risks of land contaminated with genotoxic carcinogens. This could provide an alternative approach to using QRA based on animal carcinogenicity data to set an “unacceptable” level of the contaminant in soil. It would also assist prioritisation of the resources available to remediate the land, depending on the size of the margin between estimated exposure levels and the BMDL10 (the lower confidence limit on the benchmark dose associated with a 10% response).

Before pursuing this approach, we consider that it would be helpful if the COC could consider in detail the methodology used to derive the BMDL10 and the Department of Health Toxicology Unit at Imperial College has prepared the attached discussion paper which considers this in detail and carries out a illustrative exercise for 3 genotoxic soil contaminants (hexavalent chromium, benzo(a)pyrene and 1,2-dichlorethane).

Two main issues arise from the attached paper:

1. There is the question of which of several models should be used to derive the benchmark dose to be recommended for use by practioners in the field. This is discussed in paragraph 4 of the attached paper and the COC’s advice on this point would be welcome.
2. Secondly, for each chemical, BMDL10s have been derived for all carcinogenicity endpoints for which there is a statistically significant increase in neoplasms. Where a chemical produces increases in several tumour types, this results in a number of BMDLs. In the paper, only the lowest has been used to calculate the MOE. Does the committee consider that this, conservative approach is the right one or is there another approach which could be used?

Secretariat  
October 2007

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

### FURTHER CONSIDERATION OF THE MOE APPROACH

#### Introduction

1. At the November 2006 and July 2007 COC meetings, the Committee agreed that the Margin of Exposure (MOE) approach for prioritisation of risks could be used to aid risk managers to prioritise the risks of genotoxic carcinogens and to communicate those risks to the public (CC/06/20; CC/07/08). Members agreed that this could be done using a system of banding of MOE values. To date, the committee have discussed worked examples from a number of publications on food-borne genotoxic carcinogens (O'Brien et al, 2006, EFSA<sup>1</sup>, 2005 and JECFA<sup>2</sup>, 2005). Previously, members supported an extension of the use of the MOE and banding approach to genotoxic carcinogens that are environmental contaminants. A number of soil contaminants, including hexavalent chromium, 1,2-dichloroethane and benzo[a]pyrene, were chosen for this exercise.

2. The Benchmark Dose (BMD) method was evaluated using the USEPA<sup>3</sup> BMD software. Version 1.4.1 was used for the modelling performed in this paper. The BMDx is defined as the dose that corresponds to a specific change (x%) in an adverse response compared to the response in untreated animals (Crump, 1995). The BMD is determined by modelling a dose-response curve in the region of the dose-response relationship where biologically observable data are available. To take experimental uncertainty into consideration, the dose of interest is the lower confidence limit, usually 5%, on the benchmark dose (BMDLx). The BMDLx is defined as the point on the dose-response curve established for experimental data, corresponding to a low effect level (x=1-10%), usually 10% for incidence data (US EPA, 2000). Both dichotomous and continuous data can be evaluated with the BMD approach. Dichotomous (quantal) data describes whether an effect has occurred in an individual or not, e.g., tumour or death. The data obtained from the carcinogenicity studies described in this exercise fall into the dichotomous category. The benchmark response (BMR) is a response level used to define a BMD. For quantal responses, the BMR is expressed in terms of a percent increase in risk of adverse outcome above the background. The BMR is typically set at the lower end of the range of responses (e.g., 10% or 5% change) that can be detected experimentally. In the US EPA draft benchmark dose technical document, it is stated that an excess risk of 10% has generally been the default BMR for quantal data, as this is the minimum response that can be reliably quantified in most toxicity studies. If a study has greater than usual sensitivity, then a lower BMR can be used (US EPA, 2000). For the purposes of this exercise, a BMR of 10% was used in calculating the BMD.

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1 European Food Safety Authority

2 Joint Expert Committee on Food Additives

3 US Environmental Protection Agency

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Different types of statistical testing can be utilised to validate the degree 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. For dichotomous data, the U.S. EPA software employs the Pearson's chi-squared goodness of fit test (US EPA, 1995). This test of goodness of fit establishes whether or not an observed frequency distribution differs from a theoretical distribution. Since it is particularly important that the data be adequately modeled for BMD calculation, the US EPA (2006) recommend a minimum goodness of fit p value of  $p = 0.1$  for model acceptance. For the purposes of this exercise, a p value from the chi-squared test of  $<0.1$  was set as the rejection level for the test hypothesis of adequate model fitting.

3. Comparison of different models and selection of the model for BMDx and BMDLx calculations can be made on the basis of the Akaike information criterion (AIC) (Akaike, 1974). AIC values can be obtained using the US EPA BMDS software. Although the AIC does not enable a conclusion about "statistical significance" and does not "reject" any model, it determines how well the data support each model. A number of competing models can often fit a particular set of data adequately resulting in a range of risk estimates. These models may be essentially unrelated to each other (for example a logistic model and a probit model often do about as well at fitting dichotomous data) or they may be related to each other in the sense that they are members of the same family that differ in the number or values of certain parameters included in the model.

4. After fitting the various models and deriving associated benchmark doses, the risk manager is faced with the question of which model should be used. One way of choosing an appropriate model is to select the model with the lowest AIC value from all statistically acceptable, plausible 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 BMD on the basis that this selection is likely to be more protective. Another option is to report a range of risk estimates from those models that provide a good fit to the observed data. This option is favoured by EFSA as it provides some indication of the "model uncertainty" in each dataset. A fourth option is to average risk estimates/BMDs based on the support for each model provided by the data, as suggested by Bailer et al. (2005) and Moon et al. (2005).

### **BMD Exercise**

5. The estimated exposures from indoor air, ambient air, food and drinking water and the animal bioassay data for hexavalent chromium, 1,2 dichloroethane and benzo[a]pyrene were selected from the published literature to demonstrate the margin of exposure approach. A review of the literature of relevant animal data revealed a number of appropriate carcinogenicity studies which could be modelled using the Benchmark Dose software. Details of the carcinogenicity studies and human exposure estimates are tabulated in Annex 1. Calculations of the BMD were based on

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selected single site tumour data in animals administered the test compound for a period of  $\geq 78$  weeks. Values of the BMD10 and BMDL10 were calculated from the animal dose-response data using the EPA BMDS program following fitting of mathematical models, provided by the software, for dichotomous data, such as the gamma, multistage cancer, logistic, probit, quadratic linear and weibull models (Annex 2). Annex 2 is provided for supplementary purposes and serves only as information for members to illustrate the type of data generated by the BMDS program. We report the range of BMDL<sub>10</sub> values obtained from all statistically accepted models and the lowest value of the BMDL<sub>10</sub> was chosen in each case for the calculation of the margin of exposure (MOE). The MOE is the ratio between a defined point on the dose-response curve (reference point, BMDL10) for the adverse effect of the compound in the animal carcinogenicity study and the estimated human intake of the compound.

### **Chromium Human Exposure Estimates**

6. A number of industrial activities have lead to widespread Cr contamination within soils and natural waters. Although Cr is an essential element for humans, the hexavalent form is toxic, mutagenic, and carcinogenic. The average daily intake of chromium from food for an adult person was estimated in the range of 242–339  $\mu\text{g}/\text{d}$  (3460 – 4840 ng/kg body weight per day), with only minor amounts being contributed by drinking water, 4  $\mu\text{g}/\text{d}$  (57 ng/kg body weight per day) (Rowbotham et al., 2000). There is limited information available to indicate sources of chromium in the indoor atmosphere specifically associated with the indoor environment other than from smoking. Background indoor and outdoor chromium exposure estimates are therefore assumed to be similar at 0.02 – 0.34  $\mu\text{g}/\text{d}$  person (0.28 – 4.86 ng/kg body weight per day). Assuming that Cr(VI) constitutes between 3 and 8% of total airborne chromium (Government of Canada, 1994), adult daily atmospheric exposure estimates for hexavalent chromium are in the range of 0.0005 - 0.0300  $\mu\text{g}/\text{d}$  person (0.007 – 0.420 ng/kg bw/d).

### **Animal Bioassay for Chromium**

7. We applied the BMDS method to tumour data from a recently published NTP study (2007) on sodium dichromate dihydrate to calculate BMDL<sub>10</sub> values for hexavalent chromium. Sodium dichromate dihydrate is an inorganic compound containing hexavalent chromium (Cr VI) found in drinking water source supplies as a contaminant resulting from various industrial processes including electroplating operations, leather tanning, and textile manufacturing. Groups of 50 male and 50 female rats were exposed to drinking water containing 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dihydrate for 2 years (equivalent to average daily doses of approximately 0.6, 2.2, 6, or 17 mg sodium dichromate dihydrate/kg body weight for males and 0.7, 2.7, 7, or 20 mg/kg for females). Survival of exposed groups was similar to that of the control groups. Exposure to sodium dichromate dihydrate resulted in the development of neoplasms of the squamous epithelium that lines the oral mucosa and tongue. The incidences of squamous cell carcinoma in the oral

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mucosa of high dose male and female rats were significantly greater than those in the controls. The incidence in 172 mg/L dosed females exceeded the historical control ranges for all routes of administration, including drinking water.

8. Similarly, groups of 50 male mice were exposed to drinking water containing 0, 14.3, 28.6, 85.7, or 257.4 mg/L sodium dichromate dihydrate for 2 years (equivalent to average daily doses of approximately 1.1, 2.6, 7, or 17 mg sodium dichromate dihydrate/kg body weight). Groups of 50 female mice were exposed to drinking water containing 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dihydrate for 2 years (equivalent to average daily doses of approximately 1.1, 3.9, 9, or 25 mg/kg). Survival of exposed groups was similar to that of the control groups. The incidences of neoplasms of the small intestine (duodenum, jejunum, or ileum) were increased in exposed groups of male and female mice. The incidences of adenoma of the duodenum in males and 172 and 516 mg/L dosed females were significantly greater than those in the controls. The incidence of carcinoma of the duodenum was significantly increased in high dose females. The incidence of adenoma of the jejunum in high dose females was significantly increased compared to that in the controls. When the incidences of adenoma and carcinoma were combined (because of their oncogenic relationship) for all sites of the small intestine the incidences were significantly increased in 85.7 and 257.4 mg/L dosed males and 172 and 516 mg/L dosed females compared to those in the controls. The incidences in 57.3 mg/L dosed females exceeded the historical control ranges for all routes of administration, including drinking water.

### **1,2 Dichloroethane Human exposure estimates**

9. 1,2-Dichloroethane is a synthetic chemical and its principal use is in the synthesis of vinyl chloride monomer, and to a lesser extent in the manufacture of various chlorinated solvents. The principle source of exposure to 1,2-dichloroethane of the general population is indoor and outdoor air (< 0.03 to 0.10 µg/kg body weight per day and 0.004 to 0.020 µg/kg body weight per day, respectively with only minor amounts being contributed by drinking water (< 0.001 to 0.003 µg/kg body weight per day). Intake of 1,2-dichloroethane from food appears to be negligible (EHC 176, 1995).

### **Animal Bioassay for 1,2-Dichloroethane (1,2-DCE)**

10. In a gavage study of 1,2-DCE in rats, there were significant increases in the incidence of tumours at several sites (NCI, 1978). Osborne-Mendel rats ( $n = 50$  of each sex in exposed groups;  $n = 20$  matched controls;  $n = 60$  pooled controls) were administered time-weighted-average doses of 1,2-DCE of 47 or 95 mg/kg body weight per day in corn oil by gavage, 5 days/week, for 78 weeks, followed by 32 weeks of observation. The incidence of squamous cell carcinomas of the stomach was significantly increased in both groups of exposed males (0/60, 0/20, 3/50, and 9/50 in pooled [from concurrent studies] vehicle controls, matched vehicle controls, low-dose group, and high-dose group, respectively). There were also significant increases in the incidence of

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haemangiosarcomas in exposed males (1/60, 0/20, 9/50, and 7/50) and females (0/59, 0/20, 4/50, and 4/50). The incidence of fibromas of the subcutaneous tissue was significantly increased in exposed males (0/60, 0/20, 5/50, and 6/50). In females, there were significant increases in the incidences of adenocarcinomas and fibroadenomas (combined because of their oncogenic relationship) of the mammary gland (6/59, 0/20, 15/50, and 24/50).

11. In a similar bioassay (NCI, 1978), B6C3F<sub>1</sub> mice ( $n = 50$  of each sex in exposed groups;  $n = 20$  matched controls;  $n = 60$  pooled controls) were administered time-weighted-average doses of 1,2-DCE of 97 or 195 mg/kg body weight per day (males) and 149 or 299 mg/kg body weight per day (females) in corn oil by gavage, 5 days/week, for 78 weeks, followed by 13 weeks of observation. The incidence of hepatocellular carcinomas was significantly increased in high dose males (4/59, 1/19, 6/47, and 12/48 in pooled vehicle controls, matched vehicle controls, low-dose group, and high-dose group, respectively), although the authors noted that the increase in the incidence of this tumour could not be convincingly attributed to the test chemical, owing to the high variability of hepatocellular neoplasms among historical controls. The incidence of alveolar/bronchiolar adenomas was significantly increased in males in the high-dose group (0/59, 0/19, 1/47, and 15/48) and in both groups of exposed females (2/60, 1/20, 7/50 and 15/48); one female in the high-dose group had an alveolar/bronchiolar carcinoma. The incidence of mammary gland adenocarcinomas was significantly increased in females at both doses (0/60, 0/20, 9/50 and 7/48). The incidence of endometrial stromal polyps and endometrial stromal sarcomas (combined because of their oncogenic relationship) in females was significantly elevated at both doses (0/60, 0/20, 5/49 and 5/47) (NCI, 1978).

12. The carcinogenicity of 1,2-dichloroethane was also investigated by inhalation exposure of groups of 50 F344 rats and 50 B6C3F<sub>1</sub> mice of both sexes to 1,2-DCE vapour or clean air as control for 6 h/d, 5 d/wk and 104 wk (Nagano et al., 2006). The rats were exposed to 10, 40 or 160 ppm (v/v) 1,2-dichloroethane, while the mice were exposed to 10, 30 or 90 ppm. The 2-yr exposure to 1,2-dichloroethane resulted in a dose-dependent increase in the incidences of benign and malignant tumours, including subcutaneous fibroma, mammary gland fibroadenoma and peritoneal mesothelioma in male rats; subcutaneous fibroma and mammary gland adenoma, fibroadenoma and adenocarcinoma in female rats; liver hemangiosarcoma in male mice and bronchiolo-alveolar adenoma and carcinoma, endometrial stromal polyp, mammary gland adenocarcinoma and hepatocellular adenoma in female mice. The types of tumours and their target organs found in this study were consistent with those observed in rats and mice administered 1,2-dichloroethane by gavage in the NCI study described above.

### **Benzo[a]pyrene (B[a]P) human exposure estimates**

13. Benzo[a]pyrene occurs ubiquitously in products of incomplete combustion of fossil fuels and has been identified in ambient air, surface

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water, drinking water, waste water, and char-broiled foods (IARC, 1983). Possible sources of non-occupational exposure to B[a]P are: polluted ambient air (main emission sources: vehicle traffic, industrial plants, and residential heating with wood, coal, mineral oil); polluted indoor air (main emission sources: open stoves and environmental tobacco smoke), tobacco smoking and contaminated food and drinking-water. Inhalation of B[a]P from indoor air was calculated to range from 10 to 50 ng/d in a U.S study by Waldman et al.(1991). Intake from ambient air ranged from 0.0040 - 0.0435 µg/d person in a range of studies from Europe and the US (IPCS, 1998). From surveys conducted in six EU countries, the mean or national-averaged dietary intake of benzo[a]pyrene for an adult person was estimated in the range 0.05 to 0.29 µg/day (0.70 – 4.14 ng/kg body weight per day), with only minor amounts being contributed by drinking water (0.003- 0.030 ng/kg body weight per day) (EFSA, 2002).

### Animal Bioassay for Benzo[a]pyrene

14. We applied the BMDS method to tumour data from two studies (Culp et al., 1998 and Kroese et al., 2001) in order to calculate the MOE. In the study of Kroese et al. (2001), groups of 74 Wistar rats (per dose, per sex) were administered B[a]P (dissolved in soy oil) by gavage, 5 days a week at dose levels of 0, 3, 10, or 30 mg B[a]P/kg bw. Controls received the vehicle only. Of these, 52 animals (per dose, per sex) were subjected to this regime for 104 weeks, i.e. for carcinogenicity testing. Tumour incidence and pathology were determined in all control animals. A dose-dependent increase in hepatocellular tumours were observed in both male and female rats treated with benzo[a]pyrene, with increases evident at the lowest dose (0/52, 4/52, 38/52, 51/52 and 0/50, 2/52, 39/52, 51/52, respectively). In a 2-year feeding study by Culp et al. (1998), groups of 48 five-week-old female B6C3F<sub>1</sub> mice received 5, 25, or 100 ppm B[a]P (equivalent to 0.65, 3.5, 15.3 mg/kg/d) in the diet. All mice, including those that died during the experiment, were subjected to full histopathologic examination to determine tumour incidence and nontumour pathology. Tumour incidence and pathology were determined in all control animals. There were highly significant dose-dependent increases in the incidences of papillomas and/or carcinomas of the forestomach squamous epithelium in mice treated with benzo[a]pyrene, the increases in the mid- and high-dose groups being statistically significant (1/48, 3/47, 36/46, 46/47). Squamous cell papillomas or carcinomas of the epithelial lining of the oesophagus were present in mice fed 25 and 100 ppm benzo[a]pyrene (0/48, 0/48, 2/45, 27/46). The incidence in the mice fed 100 ppm benzo[a]pyrene was significantly increased compared to the solvent-control group and overall there was a significant dose effect. Papillomas and/or squamous cell carcinomas of the epithelial layer on the dorsal surface of the base of the tongue were found in the mice fed 25 and 100 ppm benzo[a]pyrene (0/48, 0/48, 2/46, 23/48). The incidence in the mice fed 100 ppm benzo[a]pyrene was significantly increased compared to the solvent control group and overall there was a significant dose effect. A significant dose related trend was

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observed for squamous cell papillomas and/or carcinomas of the larynx in mice fed 25 and 100 ppm benzo[a]pyrene (0/35, 0/35, 3/34, 5/38).

### Findings and Discussion

15. For illustrative purposes, Annex 3 presents the calculated margins of exposure for the selected environmental carcinogens for exposures from air, food and drinking water. Exposure data were drawn from a number of sources including EFSA and IPCS. For the three contaminants, the lowest BMDL<sub>10</sub> value obtained from each cancer dataset and the upper and lower bound human exposure estimate were used to calculate the MOE range. The calculated margins of exposure against rodent bioassay derived BMDL<sub>10</sub> values show a wide range. At the November 2006 and July 2007 COC meetings, the committee advanced the idea of developing a system for banding MOE values. This expands on proposals for the interpretation of the magnitude of the MOE that had been made by JECFA and EFSA, where there was a consensus that an MOE greater than 10,000 indicated low concern. The COC committee broadly accepted the banding approach and thought that the banding approach, described in CC/07/08, could be adapted so that the bands were termed: “May be a concern”, “Unlikely to be a concern”, and “Highly unlikely to be a concern” as outlined below.

MOE Band	Interpretation
<10,000	May be a concern
10,000-1,000,000	Unlikely to be a concern
>1,000,000	Highly unlikely to be a concern

16. Based on estimates of human exposure from food, the margins of exposure for benzo[a]pyrene were high (MOE range of 130,000 -7,000,000), whereas the MOEs for chromium were lower, ranging from 9,100 - 90,000 (exposure to 1,2-DCE via food is negligible). Using the banding discussed by COC at its November 2006 and July 2007 meetings, long term exposure to B[a]P via the diet would be regarded as “unlikely to be a concern”, whereas such exposure to chromium would be regarded as “may be a concern”. However, it should be noted that the lowest margin of exposure for chromium was close to the lower boundary of the “unlikely to be a concern” band. There were 8 estimated MOE ranges for dietary chromium and only one had a lower bound below 10,000. The upper bound of this estimate was 12,700. Independent of banding, these data suggest that exposure to B[a]P via the diet is of less potential concern than such exposure to chromium.

17. The MOE values based on human exposure via food for benzo[a]pyrene given in Annex 3 differ from those derived recently by JECFA (JECFA, 2005) but are similar to those reported in O’Brien et al. (2006). The

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reason for the difference is that the calculations presented here and those from EFSA were based on incidence data for individual tumour types in rats and mice following oral administration of B[a]P. The JECFA BMDL<sub>10</sub> was derived from data for tumour-bearing animals in a mouse bioassay following administration of B[a]P in a mixture of PAHs in coal tar (Culp et al., 1998) where benzo[a]pyrene was used as a marker. The estimates of human intake of B[a]P from food (0.70 - 4.14 ng/kg bw/d) used here are similar to that in the JECFA paper, where a mean intake of 4 ng benzo[a]pyrene/kg bw per day and a high-level intake of 10 ng benzo[a]pyrene/kg bw per day were used in their evaluation.

18. Based on human exposure through drinking water, high margins of exposure were observed for all three contaminants, with MOEs ranging from 770,000 – 5,500,00 for chromium, 4,000,000 – 192,000,000 for 1,2-dichloroethane and 17,000,000 – 1,600,000,000 for B[a]P. Hence, chronic exposure to 1,2-DCE and B[a]P in drinking water would be considered “highly unlikely to be a concern”, if the proposed wording of the COC bands were used. In the case of chromium, 2 of 8 estimates of the MOE were slightly below the lower bound of the “unlikely to be a concern” risk band. Hence, chromium exposure via drinking might be considered as of marginally more concern than such exposure to 1,2-DCE or B[a]P.

19. Based on exposure from ambient and indoor air, high margins of exposure were found for all three contaminants. For indoor air and ambient air, the MOEs ranged from 700,000 – 34,000,000 and 840,000 - 80,000,000 for B[a]P respectively, from 71,000 - 6,400,000 and 355,000 - 48,000,000 for 1,2-dichloroethane respectively. Background indoor and outdoor chromium exposure estimates are similar and a MOE range of 11,000,000 - 1,000,000,000 was obtained for total chromium and a MOE range of 133,000,000 - 44,000,000,000 for hexavalent chromium. Long term exposure to 1,2-DCE via indoor air could be considered as “unlikely to highly unlikely to be a concern”, whereas exposure via ambient air might be considered to be “highly unlikely to be a concern”. The lower bound of only three out of 19 estimates of the MOE was below 1,000,000. The average of two of these estimates was well above 1,000,000. In the case of B[a]P and chromium, either as total or as hexavalent chromium, the risk of exposure to both indoor and ambient air could be considered as negligible. With chromium, the lower bound of all MOE estimates was well above 1,000,000. For B[a]P, the lower bound for the MOE estimates was slightly below 1,000,000 for one MOE estimate out of 6 for each of indoor and ambient air, respectively. In both cases, the average MOE estimate was well above 1,000,000.

20. MOE is a pragmatic approach that takes into account both carcinogenic potency and exposure. The availability of equally good quality carcinogenicity data and exposure estimates are necessary to ensure meaningful comparison of MOE's from different studies. The committee should note that there was limited availability/choice of long term carcinogenicity data for the three contaminants used in this BMD exercise. The confidence that can be placed in any particular MOE is also dependent on the reliability of the exposure

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assessment. MOEs for different subgroups of the population may differ because of differing exposures. A clear narrative of the underlying scientific assumptions/uncertainties in the toxicity data and in the exposure data should be provided in order to put perspective and context to the calculated MOE values.

21. The BMD software can be downloaded from the US EPA website and is quick to learn and apply. The availability of BMD software to facilitate the analysis can make modeling appear simple, but often the interpretation of the results is complex. Filipsson et al. (2003) recommended that benchmark dose modeling be performed in collaboration with a toxicologist and someone familiar with this type of statistical analysis to aid with interpretation of the results.

The Committee may wish to consider the following:

- Do Members consider that the current exercise has helped address the feasibility of banding MOE values based on the approach proposed by the FSA for the presentation of advice to wider audiences?
- Do Members support extending the use of the MOE and banding approach to genotoxic carcinogens which are environmental contaminants, for example, soil contaminants?
- Do Members have any comments on approaches to data presentation and interpretation, for example the use of ranges for individual MOE estimates and the interpretation of a range of MOE estimates?

**Secretariat  
October 2007**

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