Estimated Total Annual Respondent Non-hourly Cost Burden: $2,413. There are no capital start-up, maintenance costs, or recordkeeping costs associated with this information collection. However, the USPTO estimates that the total annual (non-hour) cost burden for this information collection, in the form of filing fees and postage is $2,413.

Filing Fees

The application in this information collection has two associated filing fees, resulting in $2,240 in annual non-hourly cost burden.

Item No.	Fee code	Item	Estimated annual responses (a)	Filing fee ($) (b)	Non-hourly cost burden (a) × (b) = (c)
1	6991 6992	Filing an application for recordal of insignia or renewal/reactivation of recordal.	90	$20	$1,800
1	6993 6994	Surcharge for filing six months after the expiration date—Filing an application for recordal of insignia or renewal/reactivation of recordal.	22	20	440
	Totals		112		2,240

Postage Costs

Although the USPTO prefers that the items in this information collection be submitted via email, responses may be submitted by mail through the United States Postal Service (USPS). The USPTO estimates that 17 items will be submitted in the mail. The USPTO estimates that the average postage cost for a mailed submission, using a Priority Mail legal flat rate envelope, will be $10.15. Therefore, the USPTO estimates the total mailing costs for this information collection at $173.

IV. Request for Comments

The USPTO is soliciting public comments to:

(a) Evaluate whether the collection of information is necessary for the proper performance of the functions of the Agency, including whether the information will have practical utility;

(b) Evaluate the accuracy of the Agency's estimate of the burden of the collection of information, including the validity of the methodology and assumptions used;

(c) Enhance the quality, utility, and clarity of the information to be collected; and

(d) Minimize the burden of the collection of information on those who are to respond, including through the use of appropriate automated, electronic, mechanical, or other technological collection techniques or other forms of information technology, *e.g.,* permitting electronic submission of responses.

All comments submitted in response to this notice are a matter of public record. The USPTO will include or summarize each comment in the request to OMB to approve this information collection. Before including an address, phone number, email address, or other personally identifiable information (PII) in a comment, be aware that the entire comment—including PII—may be made publicly available at any time. While you may ask in your comment to withhold PII from public view, the USPTO cannot guarantee that it will be able to do so.

Justin Isaac,

Information Collections Officer, Office of the Chief Administrative Officer, United States Patent and Trademark Office.

[FR Doc. 2024–08660 Filed 4–22–24; 8:45 am]

BILLING CODE 3510–16–P

CONSUMER PRODUCT SAFETY COMMISSION

[Docket No. CPSC–2023–0032]

Notice of Availability: Supplemental Guidance for CPSC Chronic Hazard Guidelines

AGENCY: U.S. Consumer Product Safety Commission.

ACTION: Notice of availability.

SUMMARY: The Consumer Product Safety Commission (Commission or CPSC) is announcing the availability of final supplemental guidance for its Chronic Hazard Guidelines. This supplemental guidance contains two guidance documents, one for the use of benchmark dose methodology in risk assessment and the other for the analysis of uncertainty and variability in risk assessment.

ADDRESSES: *Docket:* For access to the docket to read background documents or comments received, go to *www.regulations.gov* and insert the docket number, CPSC–2023–0032, in the ''Search'' box, and follow the prompts.

FOR FURTHER INFORMATION CONTACT: Eric Hooker, Directorate for Health Sciences, U.S. Consumer Product Safety Commission, 5 Research Place, Rockville, MD 20850; telephone: (301) 987–2516; email: *ehooker@cpsc.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

In 1992, the Commission issued guidelines for assessing chronic hazards (Chronic Hazard Guidelines or Guidelines) under the Federal Hazardous Substances Act (FHSA), 15 U.S.C. 1261–78, including carcinogenicity, neurotoxicity, reproductive/developmental toxicity, exposure, bioavailability, risk assessment, and acceptable risk. 57 FR 46626. In August 2023, the Commission issued a Notice of Availability containing Proposed Supplemental Guidance for CPSC Chronic Hazard Guidelines and asked for comments on the proposed guidance. 88 FR 57947. After reviewing those comments, the Commission is now issuing the final supplemental guidance contained below in sections III and IV.[1]

Determining whether a product is or contains a hazardous substance involves scientific analysis, legal interpretation, and the application of policy judgment. The Guidelines are intended to assist firms in identifying products that present chronic hazards, to meet their labeling obligations under the FHSA and the Labeling of Hazardous Art Materials Act (LHAMA). 15 U.S.C. 1277. They are not binding on industry or the Commission. Indeed, chronic toxicity may be established in various ways. The Commission may determine that a product is a hazardous substance due to a chronic hazard based on any evidence that is relevant and material to such a determination.

[1] On April 12, 2024, the Commission voted 5–0 to approve publication of this notice. Commissioners Feldman and Dziak submitted a joint statement, available at *https://www.cpsc.gov/About-CPSC/Commissioner/Douglas-Dziak-Peter-A-Feldman/Statement/Statement-of-Commissioners-Peter-A-Feldman-and-Douglas-Dziak-on-CPSC-Chronic-Hazard-Guidelines.* Commissioner Trumka submitted a statement, available at *https://www.cpsc.gov/About-CPSC/Commissioner/Richard-Trumka/Statement/CPSC-Revamps-Chronic-Hazards-Guidelines-Making-It-Easier-to-Protect-You-From-Toxic-Chemicals-in-Your-Home.*

For example, peer-reviewed scientific studies by third parties and toxicity assessments from CPSC's peer agencies may be relevant and material evidence to establish chronic toxicity and that a substance is a ''hazardous substance'' under the FHSA. Likewise, evidence from third parties may be useful to determine chronic toxicity. For instance, third party studies may indicate that chronic adverse health effects are associated with foreseeable levels of consumer exposure, allowing the Commission to conclude that the FHSA's criteria for a ''hazardous substance'' are satisfied. Other cases, however, may require original research to fill gaps in knowledge.

In addition, while the Guidelines describe certain toxic endpoints, they do not limit the toxic endpoints the Commission may consider. The Commission may consider all forms of personal injury or illness as potential toxic endpoints.

The Chronic Hazard Guidelines, which should be understood as a set of best practices, are not mandatory for the Commission or for stakeholders. The guidelines describe methods that CPSC staff may use to assess chronic hazards under the FHSA. Furthermore, the guidelines are intended to be sufficiently flexible to incorporate the latest scientific information, such as advances in risk assessment methodology. Risk assessors may deviate from the default assumptions described in the guidelines, provided that their methods and assumptions are documented, scientifically defensible, and supported by appropriate data as indicated in section VI.A.2 of the preamble of the guidelines. 57 FR 46633. However, given that the guidelines represent an available set of best practices, risk assessors are encouraged to use the information and approaches outlined therein where appropriate.

In the years since the guidelines were issued, there have been numerous advances in the basic science underlying the guidelines, such as the use of transgenic animals to elucidate mechanisms of carcinogenicity and toxicity. There also have been several changes in the practice of risk assessment, including wider acceptance and use of risk assessment methods such as the benchmark dose approach and probabilistic exposure assessment. Therefore, CPSC is finalizing two guidance documents to supplement the 1992 guidelines.

The first supplement provides guidance for the application of benchmark dose methodology (BMD) to risk assessment. This supplement discusses an alternative to the traditional approach described in the original guidelines for estimating acceptable daily intakes (ADIs) for carcinogenic and other hazards, such as neurotoxicological or reproductive/developmental hazards. The second supplement is guidance for the analysis of uncertainty and variability, including use of probabilistic risk assessment methodology, which is most relevant to exposure assessment.

Like the 1992 guidelines, the supplemental guidance documents are not mandatory. Rather, they describe methods that CPSC staff and manufacturers may use to evaluate chronic hazards. The guidelines are intended to assist manufacturers in complying with the requirements of the FHSA and to facilitate the use of reliable risk assessment methodologies by both manufacturers and CPSC staff.

II. Response to Comments

In response to the Commission's August 2023 Notice of Availability of the proposed supplemental guidance, the Commission received two comments. The commenters were the National Center for Health Research (NCHR) and one individual, Albert Donnay. They had questions about the timing of the release of the guidance, technical details of benchmark dose modeling, how to determine risk assessment approaches in the context of the guidance, and the citation of references after the 2008 peer review of the supplemental guidance.

Comment 1: NCHR noted that time has passed since a draft of the Supplemental Guidance was peer reviewed in 2008.

Response 1: Although the Supplemental Guidance might have been finalized earlier, the methods and approaches described in the Chronic Hazard Guidelines and the Supplemental Guidance are neither mandatory nor proscriptive. Publication of the Supplemental Guidance does not change the Commission's substantive policies. As before, risk assessors are encouraged to use modern and applicable approaches to identify and quantify consumer product chemical hazards and risks, provided that methods and assumptions are documented, scientifically defensible, and supported by appropriate data.

Comment 2: NCHR questioned whether it is appropriate to recommend using linear modeling of benchmark dose assessment for all carcinogens and non-carcinogens.

Response 2: Linear dose-response modeling describes a constant proportional increase in a biological response (*e.g.,* toxicity) as the dose or exposure level increases and is often used for low dose cancer risk assessments. Contrary to this comment, the supplemental guidance does not recommend linear modeling for *all* carcinogens and noncarcinogens. For non-cancer endpoints, the supplemental guidance specifically states that ''a non-linear dose response is generally presumed. . . .'' On the other hand, for cancer risk, the Commission prefers linear extrapolation to the background level from the BMD as a point of departure (PoD). However, the guidance also describes that a non-linear dose response with use of uncertainty factors may be used if there is convincing evidence that the dose response is non-linear at low doses. The preference for the linear assumption is based on theoretical considerations of carcinogenicity, as well as modeling considerations, which are described in detail in the Chronic Hazard Guidelines and the Supplemental Guidance. The supplemental guidance also states that risk assessors may use methods other than those described in the guidelines, provided that their methods and assumptions are documented, scientifically defensible, and supported by appropriate data.

Comment 3: NCHR requested more specific guidance as to the conditions under which it would be acceptable to deviate from the assessment methodology outlined in the guidance.

Response 3: CPSC's reference to the use of professional judgment is based on its expectation that the risk assessor has the training, expertise, and experience to analyze datasets using the tools and approaches that are most appropriate and relevant to meet the needs and requirements for each assessment. The Commission understands that a variety of tools, models, and methods currently exist, and anticipates further advancements in this science. Thus, the supplemental guidance reiterates that expertise and professional judgment are required when applying the guidelines and emphasizes that the guidelines cannot be applied mechanically.

Comment 4: Albert Donnay asked when these supplements were most recently revised, what contractor(s) contributed to the latest revisions if they were not done solely by staff, and how many independent scientists with expertise in either BMD or PRA reviewed the post-2008 revisions before they were published in the FR.

Response 4: After the peer review of the supplements conducted in 2008, CPSC staff revised and updated the proposed supplements to incorporate discussion of more recently released

tools, such as benchmark dose software packages and supporting guidance documents from the U.S. Environmental Protection Agency (EPA) and the Dutch National Institute for Public Health and the Environment (RIVM). In addition, CPSC staff updated the references in the draft supplemental guidance to include literature published after 2008 and assessed that the more recent literature did not indicate a need for revision of the draft supplemental guidance or for additional independent review. These updates were performed by CPSC staff without participation of contractors.

Having considered the comments, the Commission is finalizing the guidance as proposed, without changes. The Final Supplemental Guidance for the Use of Benchmark Dose Methodology in Risk Assessment and Final Supplemental Guidance for the Analysis of Uncertainty and Variability in Risk Assessment are stated in sections III and IV.

III. Final Supplemental Guidance for the Use of Benchmark Dose Methodology in Risk Assessment

A. Background

In 1992, the U.S. Consumer Product Safety Commission (CPSC) issued guidelines for assessing chronic hazards under the Federal Hazardous Substances Act (FHSA) and the Labeling of Hazardous Art Materials Act (LHAMA), including carcinogenicity, neurotoxicity, reproductive/developmental toxicity, exposure, bioavailability, risk assessment, and acceptable risk (CPSC 1992). 57 FR 46626. The chronic hazard guidelines, which are not mandatory for CPSC or stakeholders, are intended as an aid to manufacturers in making their determination of whether a product is a hazardous substance due to chronic toxicity, and thus would require labeling under the FHSA. The guidelines describe methods that CPSC staff use to assess chronic hazards under the FHSA. Furthermore, the guidelines are intended to be sufficiently flexible to incorporate the latest scientific information, such as advances in risk assessment methodology. Risk assessors may deviate from the default assumptions described in the guidelines, provided that their methods and assumptions are documented, scientifically defensible, and supported by appropriate data. However, given that the guidelines represent an available set of best practices, risk assessors are encouraged to use the information and approaches outlined therein where appropriate, and other methods will be reviewed by staff to determine acceptability.

In the years since the guidelines were issued, there have been numerous advances in the basic science underlying the guidelines, such as the use of alternative methods to elucidate mechanisms of carcinogenicity and toxicity. There also have been several changes in the practice of risk assessment, such as in the assessment of risks to children, as well as wider acceptance and use of risk assessment methods such as the benchmark dose approach and probabilistic exposure assessment. Therefore, CPSC staff-initiated reviews of the existing chronic hazard guidelines and is recommending additions or changes, as appropriate. The purpose of this document is to describe supplemental guidance for the application of the benchmark dose approach in risk assessment.

The current scientific knowledge regarding the risk assessment of chronic hazards is such that the guidelines cannot be applied mechanically (CPSC 1992, section VI.A.2, page 46633). Rather, considerable expertise and professional judgment are required to apply the guidelines properly. Furthermore, the volume of scientific literature on chronic hazard risk assessment, in general, and the benchmark dose, in particular, is extensive. Therefore, the discussion and guidance described below are not intended to explain how to perform chronic hazard risk assessments using the methods described. The guidelines assume that the reader has the necessary expertise. In addition, the discussion presented here is necessarily brief. The risk assessor is referred to the literature on benchmark dose, only a portion of which is cited here.

B. Discussion

The benchmark dose (BMD) approach (Crump 1984a; Crump et al. 1995) is an alternative to the traditional method of deriving acceptable daily intake (ADI) [2] levels by using no observed adverse effect levels (NOAELs) [3] and lowest observed adverse effect levels (LOAELs). The BMD may be used for both cancer and non-cancer endpoints, quantal or continuous data, and animal or human data. The BMD is an estimate of the dose level for a particular response. For example, the BMD_{10} is the best estimate of the dose at an excess risk (risk over background) of 10%, and the $BMDL_{10}$ is the lower confidence limit (LCL) of the BMD_{10}. The benchmark response (BMR) level is the response level selected for deriving an ADI level or cancer unit risk (slope factor).[4] The BMR is within or near the observable range of the bioassay used to derive the ADI or unit risk. Typically, selected BMR's range from 1% to 10% excess risk. To derive an ADI for non-cancer endpoints, the BMD is divided by the same uncertainty (safety) factors that are normally applied to the NOAEL. For cancer risk, the BMD is used as a ''point of departure'' (PoD) for linear extrapolation to the background level (EPA 2005). However, uncertainty factors may be applied for cancer risk if there is convincing evidence for a non-linear dose response at low doses.

1. Advantages of the BMD Approach

The advantages of the BMD approach have been described in detail elsewhere (Barnes et al. 1995; Crump 1984a; Crump et al. 1995; Gaylor et al. 1998; EPA, 2012; Filipsson et al. 2003). For example, the NOAEL and LOAEL are limited to the doses tested in the bioassay. In contrast, the BMD is not limited to the doses tested in the bioassay. Thus, the BMD provides a more consistent basis for comparisons between studies that did not use the same dose levels.

The true (parametric) value of the BMD is independent of the study design, such as the number of animals per dose group, *n.* However, the NOAEL is sensitive to *n.* The NOAEL is not a threshold, although it is frequently regarded as such. Rather, it is more appropriate to regard the NOAEL as a limit of detection. The incidence of adverse effects may be as high as 20% at the NOAEL. A given dose level may be a NOAEL in a study with small *n* if the incidence is not significantly different from background. However, the same dose in a larger study may be a LOAEL due to the increased sensitivity resulting from a larger *n.* The traditional NOAEL approach ''rewards'' studies with small *n,* by resulting in higher (*i.e.,* less protective) NOAELs. Conversely, the traditional approach ''penalizes'' studies with larger *n,* by resulting in lower (more protective) NOAELs. Thus, the traditional method is a disincentive to performing better, larger studies. In contrast, the BMD is essentially independent of *n* and,

[2] The ADI is an estimate of the amount of a chemical a person can be exposed to on a daily basis over an extended period of time (up to a lifetime) with a negligible risk of suffering deleterious effects. The ADI is roughly equivalent to a ''reference dose'' or ''tolerable daily intake.''

[3] In the chronic hazard guidelines, ''NOEL'' is used synonymously with ''NOAEL,'' because only adverse effects are relevant under the FHSA.

[4] The term ''unit risk'' is used synonymously with ''slope factor'' (CPSC 1992).

therefore, does not penalize studies with a larger *n*.

The BMD approach may account for variability in the bioassay. If the BMDL is used, larger studies tend to have smaller confidence intervals. Thus, larger studies are generally rewarded, because a smaller confidence interval leads to a higher BMDL. In contrast, poorly designed studies with inadequate sample size are penalized by having larger confidence intervals, leading to a lower BMDL.

The BMD accounts for the slope and shape of the dose response curve and uses all of the dose response data from the study. In contrast, the NOAEL or LOAEL relies on the response at only one dose level. Thus, information on the slope and shape of the dose response curve is ignored.

With the BMD approach, the methodology is the same regardless of whether a NOAEL is established. An additional uncertainty factor that is generally applied when using the LOAEL is not required in a BMD analysis, because the BMD can still be estimated even if a NOAEL has not been established.

While there are several advantages to the BMD approach, the principal disadvantage is the added complexity of the methodology. BMD methods require expertise in statistics, as well as toxicology. The additional steps involved in the analysis also increases the number of decision points, such as the choice of BMD and mathematical model, which require professional judgment. This, in turn, increases the number and possibly the range of possible ADI values from a given data set and may lead to areas of disagreement among risk assessors.

2. BMD Methodology

While the overall BMD approach is straightforward, there are many factors that must be considered in applying BMD methods in risk assessment, including the selection of the most appropriate endpoint and data set, dose response model, statistical methods, and selection of the BMD. Each of these factors requires knowledge of toxicology and risk assessment, as well as professional judgment.

a. Selection of the Endpoint and Data Set to Model

Initially, the selection of the critical study and endpoint to model is similar to the traditional approach. The study should be well-designed and executed, with an adequate number of animals and doses, and a statistically significant effect (CPSC 1992, sections VI.C.3.a, p. 46639; VIC.3.b, p. 46640; VI.D.2.a, p. 46642; and VI.D.3.b, p. 46643). There should be a dose where there are no observed adverse effects, *i.e.,* at or near the NOAEL. The selection of the critical endpoint is based, in part, on the judgment of the toxicologist or pathologist regarding the biological significance of the endpoint. When multiple studies, multiple endpoints, or multiple species are available, generally the most sensitive dose response is used (CPSC 1992, section F.4.b.ii, p. 46656).

It should be noted that the study with the lowest NOAEL will not necessarily lead to the lowest BMD, because the BMD also depends on the slope of the dose-response curve. Therefore, all relevant endpoints and studies should be modeled (Filipsson et al. 2005) to ensure that the lowest BMD is identified.

Additionally, the data set must be amenable to modeling. That is, there should be a steadily increasing dose response that is not saturated at the high doses. If none of the available dose response models can adequately fit the data (see below), the BMD approach cannot be used.

b. Selection of the Dose Response Model

The BMD approach is essentially a curve-fitting exercise. The choice of the dose-response model does not require any knowledge of the mode of action. Thus, the form of the model is not necessarily prescribed or dictated by any specific information about the studied activity, provided that it adequately describes the data. In some instances, however, mechanistic information may suggest a particular model, such as the Hill model when cooperative binding is observed.

A variety of dose-response models have been used to estimate the BMD (Crump 1984a; Crump et al. 1995; EPA 2022; Filipsson et al. 2003; Gaylor et al. 1998). The BMD approach may be applied to either quantal (dichotomous) or continuous data. Incidence data, such as the number of animals with a certain adverse effect, are quantal. Serum enzyme or hormone levels are examples of continuous data. Generally, quantal and continuous data require different, though related, dose response models. Nested quantal models may be used with developmental studies to evaluate effects within and between litters.

Dose response models for quantal data include linear (one-hit), quadratic, gamma multi-hit, Weibull, polynomial (multistage), logistic, log-logistic, probit, and log-probit models. These are slightly modified versions of the dose response models that have been used for cancer risk assessment (compare Crump 1984b; Zeise et al. 1987). The linear, quadratic, and Weibull models are essentially subsets of the polynomial model. Therefore, some or all of these models may yield similar results for certain data sets, such as when the dose response is linear. Dose response models for continuous data include linear, quadratic, linear-quadratic, polynomial, power, and Hill models. In addition, nested models are available for developmental studies. The mathematical forms of the models are described in detail elsewhere (Crump 1984a; Crump et al. 1995; EPA 2022; Filipsson et al. 2003; Gaylor et al. 1998).

In applying the BMD approach to non-cancer endpoints, the dose response models are not used for low-dose extrapolation. Thus, in contrast to cancer risk assessment, there is no need to consider the shape of the curve at low doses. Therefore, the choice of dose response model depends, in large part, on the goodness of fit. That is, the model (or models) selected must adequately describe the data. A model is generally rejected if the probability based on chi-square is less than 0.05. In other words, if the probability that the deviation of the data from the model is due to random variability is less than 0.05, the model does not adequately describe the data. Depending on the data set, multiple models may provide a similar global fit to the data. In this case, the local fit in the low-dose range, that is, the doses nearest the BMR, may be considered. In practice, different models often result in roughly similar BMDs, provided that they adequately describe the data. In any case, the results from different models and the choice of model should be discussed.

In some cases, it may be necessary to exclude high dose data from the model fitting procedure, to improve the goodness of fit. Data at the highest doses of a multiple dose bioassay may be considered to be less informative for the purpose of low dose extrapolation, especially in cases where the responses plateau at the high doses. Therefore, high dose groups may be systematically eliminated until the fit is acceptable (Anderson 1983).

In other cases, such as when a non-monotonic dose response is observed, none of the dose response models may be able to fit the data adequately. When this occurs, the BMD approach should not be used. While the NOAEL/LOAEL approach could still be applied, the quality of the study should be given careful consideration. It may not be appropriate to derive an ADI by any method from such a data set.

The steps for estimating the BMD may be summarized as follows:

- Select the bioassay(s) and endpoint(s) to model.
- Determine whether the data are quantal or continuous.
- Fit the bioassay data set(s) to several dose response models and determine the goodness of fit. Calculate multiple BMDs, including maximum likelihood estimates (MLEs) of risk and confidence limits. Graph the results.
- Select which model to use for determining the ADI. Generally, the model giving the best fit is used. If multiple models fit the data well, the local fit near the BMR may be considered. In some cases, the choice of model may be based on mechanistic considerations. If no model fits the data adequately, the BMD approach should not be used.
- If multiple endpoints or bioassays are modeled, select which to use for determining the ADI. The most sensitive dose response is generally used (CPSC 1992, section F.4.b.ii, page 46656). Other factors, such as severity of the effect may also be considered.
- Select which BMD (BMR) to use for deriving the ADI.
- Discuss and explain all of the decision points in the preceding steps.

c. Statistical Methods

Various types of software may be used to estimate the BMD/BMDL. The U.S. Environmental Protection Agency (EPA) has developed Benchmark Dose Software (BMDS) specifically for this purpose (EPA 2022). The BMDS and associated documentation are in the public domain and may be downloaded from the EPA website. Software is also available from the Netherlands Ministry of the Environment (RIVM 2021) and Shao and Shapiro (2018). Various other statistical software packages (*e.g.,* SAS, and R) may also be used. Likelihood methods are generally preferred for estimating the BMD and confidence limits (Crump 1984a; Crump and Howe 1985; Crump et al. 1995; Gaylor et al. 1998; EPA 2001). Goodness of fit is typically based on the chi-square distribution.

As with cancer risk assessment, CPSC staff prefers to use extra risk, rather than additional risk, as a measure of the risk over background. Extra risk applies Abbott's correction, so that animals which already have a given lesion from background processes are not considered at risk for an exposure-induced lesion of the same type. The numerical difference between extra risk and additional risk is small, provided that the background risk is sufficiently low (<0.25). Extra risk (Crump and Howe 1985) is defined by:

$$P_E = \frac{P_D - P_0}{1 - P_0}$$

where:

P_E is the extra risk, P_D is the risk at dose D, and P_0 is the background dose.

Additional risk is defined by:

$$P_A = P_D - P_0 \qquad (2)$$

where:

P_A is the additional risk.

d. Selection of the Benchmark Dose (BMD)—Quantal Data

The ADI is the dose at which the risk of an adverse effect is considered negligible. Because such risks cannot be directly measured, this requires assumptions about the shape of the dose response curve in the low dose region. For cancer, there are theoretical reasons for assuming a linear response at low dose, such as the probability that a given chemical will interact with background processes or other chemicals (CPSC 1992, VI.F.3.b.ii, page 46654). For non-cancer endpoints, a non-linear dose response is generally presumed, although the shape and slope of this curve outside of the observable range is unknown.

The selection of the BMD has been based on the following considerations: (i) The BMD should be within or near the observable range of the bioassay. (ii) It is roughly the dose at which a statistically significant effect may be observed in the bioassay (Crump et al. 1995). Thus, BMD's of 5% to 10% over background are typically used for quantal data, assuming that there is an adequate number of animals and the background level is not exceptionally high. (iii) The BMD approach is an alternative to deriving the ADI from a NOAEL. The BMD has generally been selected to approximate the NOAEL (Crump et al. 1995). Thus, the study selected for estimating the BMD should include a dose at or near the NOAEL. Other factors, such as the shape of the dose response curve or the study design (*e.g.,* CPSC 2001, 2002), may be considered on a case-by-case basis. For example, it may be desirable to select a BMD that is reflective of nonlinearity or an inflection point in the dose response curve (Murrell et al. 1998).

It is important to keep in mind that the selection of a BMD is part of the overall risk assessment process, which includes the selection of the critical endpoint and uncertainty factors, among other things. The overall process is equally as important as the individual steps. For example, the risk assessor might consider applying different uncertainty factors, depending on the BMD selected. That is, consideration could be given to larger or additional uncertainty factors if the BMD is higher than is typical, or to smaller uncertainty factors if the BMD is exceptionally low.

Numerous authors (Barnes et al. 1995; Crump 1984a; Filipsson et al. 2003) and the EPA (EPA 2005) generally recommend using the 95% lower confidence limit (LCL) of the benchmark, typically the $BMDL_{05}$ or $BMDL_{10}$. This generally satisfies the criteria listed above. In a typical bioassay, the LCL is within or near the observable range, it is near the lowest detectable response, and it is roughly equivalent to the NOAEL. Using the LCL takes into account the uncertainty in the bioassay and tends to reward larger or better studies, which generally have narrower confidence intervals. On the other hand, it has been argued that using the LCL rather than the best estimate (maximum likelihood estimate or MLE) leads to a BMD that may depend more on experimental uncertainty than on the dose response itself (Murrell et al. 1998). Thus, using the LCL tends to defeat one of the principal advantages of the BMD approach, which is to make use of the

shape and slope of the dose-response curve in the analysis.

While the choice of the BMD should be made on a case-by-case basis, it is desirable to have a default value for the purpose of consistency across different chemicals, endpoints, and risk assessors. However, even if the default value is used, the risk assessor must evaluate whether the default is appropriate in a given case, using the criteria described above. Risk assessors have most frequently used $BMDL_{05}$ or $BMDL_{10}$ to derive ADIs (or RfDs) (see above). The Chronic Hazard Advisory Panel (CHAP) convened by CPSC (CPSC 2001) and CPSC staff (CPSC 2002) used the BMD_{05} to set an ADI level for diisononyl phthalate. Health Canada also uses the BMD_{05} to set tolerable intake levels. One advantage of using the MLE is that it is more reflective of the shape of the dose response than the LCL (Murrell et al. 1998).

For cancer risk assessment, CPSC prefers to use the MLE risk (see below). However, as currently applied, the ADI is not regarded as a numerical estimate of risk, as is the case for cancer risk. Rather, it is regarded as a regulatory threshold, that is, a ''negligible risk level'' or ''virtually safe dose.'' Therefore, the reasons for using the MLE to estimate cancer risk do not necessarily apply to ADIs. This conclusion may change in the future, if true risk-based approaches are applied to non-cancer endpoints.

At the present time it seems reasonable to use the BMD_{05} (*i.e.,* the MLE) rather than the $BMDL_{05}$ (*i.e.,* the LCL) as a default value, subject to the limitations discussed above. This is consistent with the CPSC approach to estimating cancer risk and with previous CPSC applications of the BMD approach. In addition, the MLE better reflects the shape of the dose response, as compared to the LCL.

e. Selection of the Benchmark Dose (BMD)—Continuous Data

For continuous data, the BMD value is generally a level that is considered ''adverse.'' This is a matter of professional judgment by health scientists, such as toxicologists and pathologists, and must be determined on a case-by-case basis. As discussed in the previous section on ''Selection of the Benchmark Dose (BMD)—Quantal Data,'', the MLE value is preferred for risk assessment. In instances where there is no consensus on what constitutes an adverse effect, some risk assessors have used a relative change in the endpoint, such as a change of one standard deviation.

3. Cancer Risk Assessment

The multistage model (Crump 1984b) has been preferred by most federal agencies for cancer risk assessment. The multistage model is defined by:

$$P_D = 1 - e^{-[q_0 + q_1 D + q_2 D^2 \ldots q_9 D^9]} \quad (3)$$

where:

D, dose; P_D, cancer risk at dose D; and $q_0 \ldots q_9$, parameters to be fitted by the model.

The EPA has preferred to use the upper confidence limit (UCL) of the estimated risk, while CPSC staff uses the MLE risk, unless the linear term (q_1) is zero. When q_1 is zero, the UCL risk is used to ensure linearity at low doses (CPSC 1992, VI.F.3.b.ii, page 46654).

EPA began to use the BMD approach for cancer risk assessment in place of the multistage model in 2005 (EPA 2005). BMD is the preferred method for dose response assessment at EPA and other agencies (Allen et al. 2011). The default procedure is to use the BMR as a point of departure (PoD) for linear extrapolation to the background level. Uncertainty factors may be applied if there is sufficient reason to rule out a linear dose response at low doses. This procedure is analogous to the Mantel-Bryan procedure (Mantel & Bryan 1961; see also Gaylor & Kodell 1980) that was commonly used before the multistage model became available.

The BMD approach described by EPA is consistent with the default procedures used by CPSC staff under the guidelines. The primary concern of CPSC staff is that linear extrapolation should remain the default procedure for guidelines purposes. The results from using the BMD methodology and the multistage model are not substantially different when linear extrapolation is assumed. In general, a non-linear dose response with use of uncertainty factors should be used only if there is convincing evidence that the dose response is non-linear at low doses. In addition, the BMD approach offers certain advantages over the multistage model as applied by CPSC staff. While staff prefers to use the MLE estimate of cancer risk, it is necessary to use the UCL risk in cases where the linear term (q_1) is zero. By using the BMD approach, the MLE risk can be used in all cases. Thus, the process is simplified. In addition, staff use the BMD approach for non-cancer endpoints, BMD methods are used by EPA and other agencies for both cancer and non-cancer risk assessment, and the software is widely available.

The practice of the CPSC Directorate for Health Sciences (HS) is to present the best estimate of risk, rather than the upper bound, to risk managers. Thus, HS prefers the MLE of risk in cancer risk assessments (CPSC 1992, section VI.F.3.b.iii). Presenting the best estimate of risk depends on a number of considerations: (i) CPSC does not routinely define ''safe'' levels, as is frequently done by other agencies such as the Food and Drug Administration (FDA) and EPA. Rather, the need for CPSC actions based on unsafe levels are typically determined on a case-by-case basis. (ii) For typical cancer bioassays in animals, the difference between the MLE and 95% upper confidence limit (UCL) [5] is generally small, about 2- to 3-fold. (iii) The overall risk assessment process is designed to include assumptions that tend to err on the side of safety when data are lacking for a particular part of the assessment. Thus, there is always a possibility of compounding safety assumptions which could result in some cases in unrealistic estimates. Therefore, the use of the MLE rather than the UCL generally has a small effect on numerical estimates.

Therefore, the BMD approach with linear extrapolation and based on the MLE risk generally will be the default procedure for cancer risk assessments performed by CPSC staff. To further simplify the process, the multistage (polynomial) model generally will be the default model for cancer risk. However, other models that adequately describe the data may be used, as described above for non-cancer endpoints. While the choice of a PoD is not critical, the default will be the BMD_{05} (see above). Although the BMD approach will be the default procedure, the multistage model, as described above, can still be used. Risk assessors may deviate from the default assumptions described in the guidelines, provided that their methods and assumptions are documented, scientifically defensible, and supported by appropriate data (CPSC 1992, section VI.A.2).

[5] The UCL risk corresponds to the LCL dose.

The following practices are recommended when applying benchmark dose methodology:

- The BMD approach is generally the preferred method for setting ADI levels for non-cancer endpoints, provided that adequate dose response data are available.
- Appropriate dose response models and statistical methods have been described in detail elsewhere (Crump 1984a; Crump et al. 1995). Public domain software is available from EPA (EPA 2022).
- The BMD response level (BMR) used to calculate the ADI will be determined on a case-by-case basis. A range of BMR's, including best estimates and lower confidence limits, should be considered.
- As a default, CPSC staff will use the maximum likelihood estimate of the dose at which the extra risk is 5% (BMD_{05}). The same uncertainty factors currently applied to the NOAEL will be applied to the BMD.
- Several dose response models should be considered. Generally, the model that best describes the observed dose response data will be selected to derive the ADI. In addition, the ADI will generally be based on the combination of dose response model, endpoint, and study that lead to the lowest ADI.
- Risk assessors may deviate from the default assumptions described in the guidelines, provided that their methods and assumptions are documented, scientifically defensible, and supported by appropriate data (CPSC 1992, section VI.A.2). While the BMD approach is typically preferred, the traditional method based on NOAELs/LOAELs may still be used.

In addition, the BMD approach with linear extrapolation and based on the MLE risk will be the default procedure for cancer risk assessments performed by CPSC staff. The multistage (polynomial) model will be the default model for cancer risk. However, other models that adequately describe the data may be used, as described above for non-cancer endpoints. While the choice of a PoD is not critical, the default will be the BMD_{05}. Linear extrapolation from the PoD generally will be used unless there is convincing evidence that the dose response will be non-linear at low doses (CPSC 1992, VI.F.3.b.ii, page 46654). In cases where a non-linear dose response is justified, uncertainty factors may be applied as described for non-cancer endpoints. Although the BMD approach will be the preferred procedure, the multistage model, as traditionally applied by CPSC, can still be used.

C. Summary

1. Estimation of the Acceptable Daily Intake for Non-Cancer Endpoints

The following supplements the guidance on estimating acceptable daily intakes (ADIs) in the CPSC Chronic Hazard Guidelines at 57 FR 46656 (Oct. 9, 1992) in section VI.F.4.b.1.ii. This does not supersede the 1992 guidance; rather, it provides guidance on the use of newer methods for estimating ADIs.

Traditionally, CPSC staff derived acceptable daily intake (ADI) levels for non-cancer endpoints by applying safety factors (uncertainty factors) to the no-observed-effect level (NOAEL) or lowest-observed-effect-level (LOAEL). However, the benchmark dose (BMD) approach is now generally preferred over the traditional method. The benchmark dose is an estimate of the dose at a certain risk level. The BMD is estimated from a dose-response model. The advantages of the BMD approach and methods for estimating the BMD are described elsewhere (Barnes et al. 1995; Crump 1984; Crump et al. 1995; EPA 2012; Filipsson et al. 2003; Gaylor et al. 1998). Software for estimating the BMD is available from the U.S. EPA (EPA 2022) and other sources. In estimating the BMD, the risk assessor should consider the following points: (a) The dose-response model must provide an adequate fit to the data; the BMD approach may not be appropriate for all data sets. (b) Alternative dose response models should be considered, and the choice of model to derive the ADI explained. (c) Alternative endpoints and studies should also be considered, as appropriate. (d) A range of BMD response levels, including best estimates and confidence intervals should be evaluated. (e) Generally, different methods are required for dichotomous and continuous data.

The BMD selected to derive the ADI (BMD response level) is determined on a case-by-case basis. The BMD response level (BMR) must be within or near the range of experimental dose levels. As a default, for dichotomous (*i.e.,* incidence) data, the BMR will be the maximum likelihood estimate of the dose associated with an extra risk (risk over background) of 5% (BMD_{05}). For continuous data, (*e.g.,* enzyme or hormone levels), the BMD is generally based on the level considered to be an adverse effect. The default safety (uncertainty) factors described above (10-fold for human data and 100-fold for animal data) are applied to the BMD CPSC 1992, section VI.F.4.b.1.ii; Haber et al. 2018). Thus, the ADI is generally 100-fold lower than a BMD based on animal data. An additional uncertainty factor for ADIs based on a LOEL is not needed. While the BMD approach is preferred, the traditional method of applying safety factors to the NOAEL or LOAEL may still be used.

2. Estimation of Cancer Risk

The following is a supplement to the CPSC Chronic Hazard Guidelines at 57 FR 46654 (Oct. 9, 1992), section VI.F.3.b.ii.

Traditionally, CPSC staff estimated cancer unit risks (slope factors) using the multistage model (Global83). The maximum likelihood estimate (MLE) of risk was used unless the linear term (q_1) was equal to zero; in this case, the upper confidence limit of risk was used. However, the benchmark dose (BMD) approach with linear extrapolation based on the MLE risk is now generally preferred over the traditional method. The multistage (polynomial) model will be the default model for cancer risk. However, other models that adequately describe the data may be used, as described above for non-cancer endpoints. The choice of a BMD response level (BMR) or point-of-departure (PoD) will be made on a case-by-case basis. In general, the default PoD will be the MLE estimate of the dose associated with an extra risk (risk over background) of 5% (BMD_{05}). Linear extrapolation from the PoD will be used unless there is convincing evidence that the dose response will be non-linear at low doses. In cases where a non-linear dose response is justified, uncertainty factors may be applied as described for non-cancer endpoints. Although the BMD approach generally is preferred under the guidelines, the traditional CPSC approach based on the multistage model may still be used.

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IV. Final Supplemental Guidance for the Analysis of Uncertainty and Variability in Risk Assessment

A. Background

In 1992, the U.S. Consumer Product Safety Commission (CPSC) issued guidelines for assessing chronic hazards under the Federal Hazardous Substances Act (FHSA), including carcinogenicity, neurotoxicity, reproductive/developmental toxicity, exposure, bioavailability, risk assessment, and acceptable risk. The guidelines are detailed in a **Federal Register** notice. 57 FR 46626 (Oct. 9, 1992).

The chronic hazard guidelines are intended as an aid to manufacturers in making their determination of whether a product is a hazardous substance due to chronic toxicity, and thus would require labeling under the FHSA. The guidelines are not mandatory. The guidelines describe standard methods CPSC staff may use to assess chronic hazards under the FHSA. The guidelines are intended to be sufficiently flexible to incorporate the latest scientific information, such as advances in risk assessment methodology. Therefore, CPSC staff initiated reviews of the existing guidelines and is recommending additions or changes, as appropriate. The purpose of this document is to describe supplemental guidance for the analysis of uncertainty and variability in risk assessment, including the use of probabilistic techniques.

B. Discussion

In toxicological risk assessment, uncertainty is the term used to describe the lack of knowledge in the underlying science, such as when few measurements of the particular subject have been made. Uncertainty may also be associated with the choice of mathematical model used to estimate exposure or risk. Variability refers to inherent differences due to heterogeneity or diversity in the population or exposure variable, such as body weight of people in the exposed population. Variability is generally not reducible by improved measurement or further study (EPA 1997, 2014).

The theory and techniques of exposure assessment have been discussed in detail elsewhere (CPSC 1992; EPA 2014, 2019; Paustenbach 2002). Exposure may be measured directly, but, in general, an exposure assessment is often based on a mathematical model that combines several variables describing the factors that influence exposure. For example, an assessment of exposure to a chemical released into the air during use of a product will include information about the emission rate into the air, the resulting concentration of the chemical in the air, the amount of time a person using the product or spent living, working, or playing in the area, and the amount of air a person breathes during the exposure. For a given exposure scenario, the output of an exposure assessment is typically an estimate of the amount of chemical that comes into contact with the body, usually expressed per unit of body weight per day during a defined period of time or over a lifetime, although exposure may be defined in other terms.

For carcinogens, ''risk'' is the product of the exposure estimate and the dose-response value, *i.e.,* the numerical representation of cancer risk per unit of daily exposure. For non-carcinogens, the exposure estimate is compared with the ''acceptable daily intake'' (ADI), which is the level of exposure at which we expect humans not to experience harmful health effects. Although there is no numerical estimate of ''risk'' in this latter case, one may calculate the hazard index (HI), which is the ratio of the estimated exposure to the ADI (HI greater than one means that the exposure may be hazardous; HI less than one represents negligible risk).

There is no single, correct way to conduct an exposure or risk assessment for purposes of evaluating chronic hazards under the Federal Hazardous Substances Act (FHSA) or the Labeling of Hazardous Art Materials Act

(LHAMA). There are, however, important issues and concerns that are commonly encountered in risk assessment that should be considered regardless of the specific risk assessment approach. Because risk assessment is a rapidly advancing field, the discussions here should be supplemented with other information from the scientific literature, texts, and government agency guidance, as scientifically appropriate.

In most cases, the risk assessor will consider uncertainty and variability in the assessment and, at a minimum, include a discussion of the effect of uncertainty and variability on the final risk estimates. The discussion may be qualitative or it may include quantitative estimates of uncertainty and variability. Variability and uncertainty are distinct issues and should be considered separately in each analysis using appropriate statistical techniques, such as two-dimensional probabilistic analyses (Cullen and Frey 1999). In practice, however, increasingly complex analyses may not be warranted for every situation, as discussed below. In addition, the available data may not be sufficient to distinguish between variability and uncertainty or to allow statistical consideration of both issues.

Risk assessors may take one of two general approaches to conduct risk assessments: deterministic or probabilistic (stochastic) modeling. Of these, probabilistic techniques explicitly include quantification of uncertainty and variability.

Risk analyses have long been grounded on deterministic approaches. Probabilistic risk assessments have been used for many years in predicting accidents and systems failures, and in weather forecasting. Over time, probabilistic approaches have been applied to ecological and human health risk assessments (Kendall et al., 2001).

Deterministic and probabilistic modeling are both valid mathematical approaches for estimating risk. The key difference between these approaches is that deterministic modeling enters point estimates (*i.e.,* single values) for the model's inputs while probabilistic modeling uses probability distributions for some or all inputs in conjunction with statistical techniques such as Monte Carlo analysis. Consequently, the output of a deterministic assessment is a point estimate of the exposure or risk for the exposed individual or population. A probabilistic approach results in a distribution of exposure or risk estimates, which may provide additional information about the variability in the exposure of interest and the uncertainty in the analysis or of the true, but unknown risk.

Exposure and risk assessments are conducted for many different reasons, such as to answer specific questions about exposure scenarios, inform decision-making, and explore options. The ultimate application of the assessment will help determine the methodological approaches and techniques to be used. The choice of approach may be based on considerations of the available scientific information, institutional policies, time and resources available, or social implications.

Risk assessments may be iterative, *e.g.,* subject to collection of new data or refinement of existing data. Assessments may be conducted in a tiered approach, in which each analysis is based on the knowledge and resources available to the risk assessor and the needs of decision-makers and stakeholders. In general, risk analysts will work from the simple to the complex until, for example, the problem has been sufficiently characterized so that risk managers may proceed with decision-making and initiate any actions required to manage the hazard. An initial analysis may be conducted to determine whether a given exposure scenario is associated with relatively high or relatively low risk. For example, protective assumptions are sometimes used initially to characterize the level of risk. If such an assessment indicates a relatively high risk, the analyst may choose to collect more data or conduct a more complex assessment in order to verify the result before actions are taken. An initial analysis may also be used to identify insignificant exposure pathways that do not require further consideration.

In many cases, deterministic techniques may be more desirable than probabilistic methods, particularly for such early analyses that are often under time and resource constraints, because probabilistic methods can be more complex, time-consuming, and costly. On the other hand, risk managers may find that more sophisticated techniques, including probabilistic methods, are valuable in providing certain detailed information about the risks in the exposed population, to explore the uncertainty in the true, but unknown risk to an individual, or for systematically analyzing variability, uncertainty, pathways of exposure, or alternative models. The risk assessor and risk manager must consider the utility of the risk assessment result and determine the value added by each assessment choice that increases the time, cost, and complexity of the assessment.

Ultimately, a risk assessment is conducted to gain insight into the exposures and risks associated with a given scenario. See section VI.F. of the guidelines (CPSC 1992). Each assessment should be approached on a case-by-case basis, consistent with the requirements of the risk assessor and risk manager. Regardless of the risk analysis approach, the quality of the assessment depends on the quality and availability of relevant data.

In general, for a given body of knowledge, a deterministic assessment that is based predominantly on central tendency values for each of the input variables (*e.g.,* a best estimate of the available data, such as a mean or median), may provide results similar to a probabilistic assessment that is based on the same underlying information. However, risk analysts must be aware of the effects of decisions regarding the use of the available data and assumptions. For example, a deterministic analysis that uses multiple protective values rather than central values may lead to unintentionally precautious results, *i.e.,* compounding safety factors. In addition, for a distribution of data that is skewed to the right, the mean will be represented by a value in the right tail and could be considerably larger than the median. In such a case, the mean could also be considered a protective value.

The primary advantage of a probabilistic approach is the generation of information on the distribution of exposure and risk in a population, in addition to estimates of the average exposure and risk. This provides information on the range of exposures, including highly exposed individuals. However, the risk analyst must consider that sparse data or a poorly fitting distribution to the data for one or more model inputs could lead to inappropriate conclusions about the resulting distribution, particularly at the tails of the distribution, which may be most sensitive to deficiencies in the data. Further, a probabilistic model may be sensitive to correlations between input variables (*e.g.,* body weight and body surface area). Discussion of the presence of correlations and dependence among variables and their effects on the output should be included in the assessment.

Another advantage of probabilistic techniques is the ability to derive confidence intervals for exposure estimates. Thus, in addition to estimating the mean, median, and 95th percentiles of exposure, one may also estimate confidence intervals for these

estimates, expressed as X ± Y, which provides a measure of uncertainty in the estimated exposure. It also gives the risk assessor and risk manager information on the reliability of exposure estimates. Typically, the confidence intervals will be larger in the tails of the distribution, *i.e.,* confidence intervals for the 95th or 99th percentile of the distribution may be larger than the confidence interval about the mean. Therefore, whenever possible, methodology that permits the estimation of confidence intervals should be applied.

Currently, probabilistic techniques are used primarily in estimating exposure, while single point estimates are derived to describe the dose-response (*i.e.,* unit risk for carcinogens; ADI for non-carcinogens). The application of probabilistic methods to deriving unit risks and ADIs is not presently in widespread use, although this has been encouraged by the National Research Council (NRC 2009).

A distinct issue, but related to analysis of uncertainty, is sensitivity analysis. Sensitivity analysis is used to identify variables that have the largest effect on the assessment output, and general approaches and statistical techniques have been developed for both deterministic and probabilistic analyses. It is often useful to know if small changes in the values for some variables result in relatively large changes in the output. For example, such an analysis may be used to identify areas of research that could improve future risk assessments. Sensitivity analysis may also be used to focus on specific subpopulations or exposure scenarios or to identify the most important routes of exposure.

Such techniques also are useful for providing additional information in a deterministic assessment. That is, a separate sensitivity analysis can be used in conjunction with a deterministic approach to characterize the range of the most likely estimates of exposure and risk (*e.g.,* one technique is to vary key input variables, one at a time, throughout their reasonable range of values, while holding other inputs constant).

Recent exposure and risk assessments conducted by CPSC staff have used both deterministic and probabilistic methods based on the factors discussed above. For example, staff used probabilistic techniques to estimate the exposure and risk from oral intake of diisononyl phthalate by children from mouthing soft plastic toys and other objects, based on the strength of the available data (Babich 2002; Babich et al. 2004; Babich et al. 2020; Greene 2002). Yet staff used a deterministic approach with a separate uncertainty analysis to assess children's exposure to arsenic from wooden playground equipment treated with chromated copper arsenate (Hatlelid 2003), because staff concluded that the data for several key input variables were insufficient to support a probabilistic analysis. In this case, mainly central tendency values were used to estimate the exposure, and a separate uncertainty analysis provided additional information about the likely range of exposure.

Section VI.F.4.b.i. of the guidelines (CPSC 1992) states that a carcinogenic risk of one per million or less is the appropriate level for defining acceptable risk; *i.e.,* when exposure to an agent occurs, the exposed individual has an estimated excess risk of one chance in a million of developing cancer during his/her lifetime. In a deterministic analysis, one per million is compared directly with the risk value that results from the analysis. Section VI.F.1.d. of the guidelines also states that in most cases the best estimate of exposure, rather than a protective estimate, is acceptable.

Probabilistic analyses, however, result in distributions of exposure and risk. While there are no generally accepted guidelines for interpretation of results from probabilistic analyses for carcinogens, this topic has received attention (Burmaster 1996; Thompson 2002; NRC 2009). Thompson cautioned against setting ''bright-line'' criteria for use in any context, and Burmaster also argued that the risk manager must consider all the characteristics of the distribution resulting from the probabilistic assessment and not just a single point or summary statistic. As an example of how one might evaluate probabilistic results, Burmaster suggested that one might consider the skewness of the resulting risk distribution; whether the median of the distribution exceeds the one per million acceptable risk level; whether the mean exceeds one per one hundred thousand; and whether the 95th percentile exceeds one per ten thousand.

CPSC staff agrees that it generally is appropriate to consider all of the characteristics of the risk distribution (*e.g.,* the mean, median, and upper bounds values and the shape of the distribution) in judging whether or not the results represent an acceptable risk. Because of the complexity of probabilistic analyses and the diversity of possible probabilistic risk assessment results, staff assesses that it would be difficult to impose a rigid procedure for interpreting the results of probabilistic assessments. Staff recommends, however, that the one per million acceptable risk level for carcinogens currently defined in the guidelines generally should also serve as a guide for interpreting probabilistic risk assessment results. Because staff generally uses best estimates for exposure rather than upper bounds, staff assesses that interpretation of probabilistic results should be based in part on the relationship of the central tendency estimate of the resulting distribution to the one per million acceptable risk level. However, upper bound estimates of exposure (*e.g.,* 95th percentile) may provide useful information for highly exposed individuals.

Section VI.F.4.b.ii. (CPSC 1992) specifies a process for evaluating the acceptable daily intake (ADI) for neurotoxicological and developmental/reproductive agents. Staff uses these guidelines for other non-cancer effects, as well. The use of the ADI in a deterministic assessment is straightforward—the estimated exposure is compared with the ADI. As is the case with cancer risk assessment, there are no standard guidelines for interpretation of results from probabilistic analyses of non-cancer effects. Following the reasoning for cancer assessments given above, staff recommends that interpretation of probabilistic results for non-cancer effects should be based in part on comparing the central tendency estimate of the outcome to the acceptable daily intake, similar to the case for deterministic assessments. However, upper bound estimates of exposure (*e.g.,* 95th percentile) may provide useful information for highly exposed individuals.

Because the guidelines are not binding rules, they are meant to be flexible and amenable to expert judgment, as well as continuing scientific advances. The guidance for interpretation of both cancer and non-cancer exposure and risk are intended to facilitate the assessment process, but in practice, risk assessors and risk managers will consider the specific information in each case in defining acceptable exposure and risk.

C. Summary

The following supplements the guidance on exposure assessment in the CPSC Chronic Hazard Guidelines at 57 FR 46644 (Oct. 9, 1992) in section VI.F.1. It does not supersede the 1992 guidance; rather, it provides guidance on the use of probabilistic methods as an alternative method for exposure assessment.

Risk assessments may incorporate uncertainty (the lack of knowledge in the underlying science or in the choice

of mathematical model) and variability (inherent differences due to heterogeneity or diversity in the population or exposure variable). The discussion may be qualitative or include quantitative estimates of uncertainty and variability. While variability and uncertainty are distinct issues and should be considered separately in each analysis, in practice, the available data may not be sufficient to distinguish between them.

Risk assessments may be based on deterministic or probabilistic modeling. Probabilistic modeling uses probability distributions for some or all inputs in conjunction with statistical techniques such as Monte Carlo analysis, and results in a distribution of exposure or risk estimates, providing quantification of uncertainty and variability. Deterministic modeling enters point estimates for the model's inputs and results in a point estimate of the exposure or risk. Separate uncertainty analysis may be used with a deterministic approach to characterize the range of the most likely exposure and risk.

Because exposure and risk assessments are conducted for different reasons, the ultimate use of the assessment results will help determine the methodological approaches and techniques to be used. The choice of approach may be based on considerations of the available scientific information, institutional policies, available time and resources, and limitations of the methods. For example, deterministic techniques may be appropriate for initial analyses that are often under time and resource constraints; however, the use of multiple protective values in a deterministic analysis may lead to unintentionally protective results, *i.e.,* compounding safety factors. A probabilistic assessment may be used to generate information on the distribution of exposure and risk in a population or to explore the uncertainty in the true, but unknown risk to an individual, but the risk assessor must consider that sparse data or poorly fitting distributions to the data for one or more model inputs could lead to inappropriate conclusions about the results, particularly at the tails of the distribution, which may be most sensitive to deficiencies in the data. A probabilistic model may be sensitive to correlations between input variables; the presence of correlations and dependence among variables and their effects on the output should be considered.

A carcinogenic risk of one per million or less is the guidelines' default level for defining acceptable risk (16 CFR 1500.135(d)(4)(i)). In a deterministic analysis, one per million is compared directly with the risk value that results from the analysis. Interpretation of probabilistic results should be based in part on the relationship of the central tendency estimate (*e.g.,* mean or median, as appropriate for the specific distribution) to the one per million acceptable risk level, but all characteristics of the resulting distribution should be considered.

For assessment of non-carcinogens in a deterministic assessment, the exposure estimate is compared directly with the ADI, or the hazard index (HI) is calculated as the ratio of the estimated exposure to the ADI (HI greater than one means that the exposure may be hazardous; HI less than one represents negligible risk). Probabilistic results should be interpreted in part by comparing the central tendency estimate to the acceptable daily intake, but all characteristics of the resulting distribution should be considered.

The guidance for interpretation of both cancer and non-cancer exposure and risk are intended to facilitate the assessment process, but in practice, risk assessors and risk managers will consider the specific information in each case in defining acceptable exposure and risk.

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Secretary, Consumer Product Safety Commission.

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DEPARTMENT OF DEFENSE

Office of the Secretary

Defense Business Board; Notice of Federal Advisory Committee Meeting

AGENCY: Office of the Deputy Secretary of Defense, Department of Defense (DoD).

ACTION: Notice of Federal advisory committee meeting.

SUMMARY: The DoD is publishing this notice to announce that the following Federal advisory committee meeting of the Defense Business Board (''the Board'') will take place.