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Subject:
External Peer Review of Proposed Updated Public Health Goals for Cis- and Trans-1,2-Dichloroethylene in Drinking Water

Introduction

At the request of the CalEPA Office of Environmental Health Hazard Assessment (OEHHA) dated September 20, 2017, this independent written review relates to the August 2017 draft document pertaining to *Updated Public Health Goals for Cis- and Trans-1,2-Dichloroethylene in Drinking Water*. Reviewers were asked to determine whether the scientific work product is based on sound scientific knowledge, methods, and practices. The following explanatory statement was provided for each proposed updated PHG to focus the review:

[begin quote]
"1. Cis-1,2-DCE

After reviewing the literature on cis-1,2-DCE since the publication of the PHG in 2006, OEHHA concludes that liver and kidney toxicity are the primary adverse health effects associated with human exposure to this chemical. OEHHA is retaining increased relative kidney weight observed in the study by McCauley et al. (1995) as the critical endpoint for PHG derivation. OEHHA is using standard peer-reviewed methodology to derive the PHG for cis-1,2-DCE. The relative source contribution (RSC) is raised from 0.60 to 0.80.

Cis-1,2-DCE is a volatile chlorinated organic compound that is no longer in use industrially but can still be found in the environment due to the anaerobic degradation of other commonly found chlorinated solvents such as trichloroethylene and tetrachloroethylene (Mattes et al., 2010; US EPA, 2010b). The current cis-1,2-DCE PHG of 100 ppb was developed using a lowest-observed-adverse-effect level (LOAEL) of 32 mg/kg-day based on increased relative kidney weight in male rats exposed by oral gavage for 90 days (McCauley et al., 1995). No new studies were identified that could replace the critical study on which this PHG was based. However, use of benchmark dose (BMD) modeling, an updated estimation of daily water intake rate, and application of an updated intraspecies variability factor to account for sensitive individuals result in a lower proposed PHG value of 13 ppb. The RSC is the proportion of exposures to a chemical attributed to tap water, as part of total exposure from all sources (including food and air pollution). RSC values typically range from 20% to 80% (expressed as 0.20 to 0.80) and are determined based on available exposure data. The RSC is raised from 0.60 to 0.80 because cis-1,2-DCE is no longer in use and exposure to residues on food or inhalation exposures from ambient air are not expected. This results in a proposed updated PHG of 13 ppb.

2. Trans-1,2-DCE

A thorough literature search revealed no new animal toxicity studies published since the 2006 PHG. However, OEHHA is replacing the critical study and endpoint on which the 2006 PHG was based with a different critical study and endpoint. Standard peer-reviewed methodology is used to derive the PHG for trans-1,2-DCE.

Trans-1,2-DCE is the only 1,2-DCE isomer currently used in industry, primarily as a solvent and as a refrigerant. The 2006 PHG of 60 ppb for trans-1,2-DCE was based on increased relative liver weight observed in mice in a 90-day oral gavage study (Barnes et al., 1985). No new toxicity studies were identified that could be used for quantitative risk assessment. However, studies in 2007 (Landics, 2007 and Loveless et al., 2007) indicated that the antibody forming cell (AFC) assay, which measures the response of antibody producing cells of the spleen, is highly predictive of overall immunotoxicity and has been well-validated as an immunotoxicity test. Thus, OEHHA re-evaluated two immunotoxicity studies that were available at the time the 2006 PHG was developed (Munson et al., 1982 and Shopp et al., 1985). OEHHA is replacing the Barnes et al. (1985) study with Shopp et al. (1985) as the critical study because 1) the liver weight increase in Barnes et al. occurred only at the mid-dose and returned to values similar to the controls at the high dose; 2) the Shopp et al. data were amenable to BMD modeling and produced the lowest point of departure. The RSC is increased from 0.60 to 0.80 since trans-1,2-DCE is not heavily used in California and exposure to residues on food and through inhalation of ambient air are expected to be minimal. The proposed updated PHG is 50 ppb.

The Big Picture
Reviewers are not limited to addressing only the specific topics presented above, and are asked to consider the following:
(a) For each PHG update, please comment on whether OEHHA has adequately addressed all important scientific issues relevant to each chemical and to the methods applied in deriving the PHG.
(b) For each chemical reviewed, please comment on whether a relevant study useful for assessing dose-response relationship or otherwise informing the PHG development was missed.
(c) PHGs must be protective of known sensitive subpopulations. Please comment on whether each PHG is health protective.

Reviewers should also note that some proposed actions may rely on professional judgment where available scientific data are not as extensive as desired to support the statutory requirement for absolute scientific rigor. In these situations, the proposed course of action is favored over no action."
[end quote]

Scope of Review

Based on the explanatory statements quoted above, the scope of this review of trans-1,2-DCE excludes immunotoxicity and immunotoxicology, as they are not my areas of expertise. As such, the scope of comments related to BMD modeling for trans-1,2-DCE immunotoxicity presume that the critical effect is appropriate and supported.

Reviewer Comments for Cis-1,2-DCE

Benchmark Dose (BMD) Modeling

Attachment 2 of the September 20, 2017 OEHHA request notes that "OEHHA is using standard peer-reviewed methodology to derive the PHG for cis-1,2-DCE". The BMD modeling for cis-1,2-DCE indicates that $p>0.05$ was considered acceptable. This is inconsistent with US EPA (2012) guidelines which specify that $p>0.1$ is acceptable. As the updated PHG document indicates that the BMR of 1 control standard deviation was elected to be consistent with EPA (2012) guidelines, it is unclear why there is a departure from EPA guidelines for the p value. Either be consistent with EPA guidelines or specify the rationale for deviating.

BMD modeling is also presumed to occur in the range of linear kinetics such that there is a monotonic dose-response. No indication is given as to whether the modeled dose range (0 to 872 mg/kg-day) in the key McCauley et al. study is anticipated to be in the range of linear kinetics. There is evidence that 1,2-DCE displays saturation kinetics and/or inhibits its own metabolism in a dose-dependent manner. The kidney weight data did not demonstrate a clear dose-response relationship, such that many models were an unacceptable fit ($p<0.1$ according to US EPA, 2012), recognizing that a few models were an acceptable fit ($p>0.1$ according to US EPA, 2012), including the selected Hill model.

Many modelers also consider the margin (or ratio) between to the BMD_{10} and $BMDL_{10}$ to be an indicator of fit and confidence in the modeling results. The smaller the ratio, the better the fit in the dose range from which the $BMDL_{10}$ is extrapolated. The preference is for ratios < 2 (Muri *et al*., 2009). For cis-1,2-DCE, the BMD/BMDL ratio (16.35/3.76) of 4 suggest a nonoptimal fit, recognizing it is an acceptable fit according to US EPA (2012) guidelines.

Consider expressing the rat $BMDL_{10}$ as a human equivalent dose (HED) according to current US EPA (2011a) guidelines. When inadequate toxicokinetic data are available to estimate human equivalent doses, US EPA (2011a) considers the default approach to be allometric scaling (BW ¾ power). US EPA (2012) BMD guidelines also recommend that the HED be estimated and that that BMDL values be expressed as HED.

Interspecies Uncertainty Factor (UF)

Attachment 2 of the September 20, 2017 OEHHA request notes that "OEHHA is using standard peer-reviewed methodology to derive the PHG for cis-1,2-DCE" and the Introduction of the PHG update notes that "the most current risk assessment practices and methods" were applied. US EPA (2011a) recommends expressing the point-of-departure as a human equivalent dose (HED) and adjusting the interspecies UF accordingly. If inadequate toxicokinetic data are available, US EPA (2011a) considers the default approach to be allometric scaling (BW ¾ power) rather than using the animal point-of-departure. If the point-of-departure is expressed as a HED, the interspecies UF would be reduced from 10x to √10 to account for potential remaining interspecies toxicodynamic differences.

Intraspecies UF

Attachment 2 of the September 20, 2017 OEHHA request notes that "OEHHA is using standard peer-reviewed methodology to derive the PHG for cis-1,2-DCE" and the Introduction section of the PHG update notes that "the most current risk assessment practices and methods" were applied.

Use of a 30x intraspecies UF represents a departure from the default (10x) factor and should be accompanied by more explicit rationale and preferably, an empirical basis. There is more than one combination of toxicokinetic or toxicodynamic factors specified in Table A6 of Appendix III that could result in 30x and it is unclear which option(s) were elected and what data or rationale were used to support the option(s). For example, is 30x comprised of a 10x toxicokinetic factor and a √10 toxicodynamic factor, or vice-versa?

The stated rationale of "to account for sensitive individuals" is nondescript. Is this factor based on chemical-specific toxicokinetic or toxicodynamic data and derived based on current practices or recognized standard methodology, such as WHO/IPCS (2005) or US EPA (2014)? The methodology

employed (e.g., 95%ile/median, the dose metric, the sensitive population) should be specified. Conversely, if the 30x factor is based on non-chemical-specific methodology and/or is not required to be empirically derived, this should be clarified in Appendix III. Either way, there is inadequate information to determine how the proposed factor of 30x was configured and whether it is supported by the available evidence because no data or rationale were indicated. Also, with respect to terminology, RfD are intended to account for sensitive "subpopulations" rather than sensitive "individuals".

Further, Appendix III notes that "when scientific evidence is compelling, these defaults are supplanted by alternative factors or modeling results". It is unclear and potentially misleading what the word "default" refers to in this statement as well as what the word "Default" in the title of Table A6 refers to, since there appears to be both default approaches as well as alternative factors being described in Table A6. What is the OEHHA definition of "default" and which scenarios in Table A6 are defaults and which are "alternative factors"? In practice or by convention, "default" tends to refer to both a magnitude (i.e., 10x) and an approach (i.e., when there are no data). However, some of the approaches in Table A6 seem to be alternative (non-default) approaches, that do not require a chemical-specific and/or empirical basis and they can be applied in addition to (rather than supplant) default approaches. Thus, the criteria that constitute compelling scientific evidence is unclear, particularly in relation to when an alternative factor is adopted in addition to the default factor as well as when a default is supplanted by an alternative factor. There should also be a clearer distinction between science and policy.

Database Deficiency UF

The updated Database UF is now 10x (compared to 3x in the original PHG) since "There are no chronic and no developmental and reproductive toxicity studies on cis-1,2-DCE." The lack of a chronic study is already addressed with the 10x Subchronic Extrapolation UF and thus it is unconventional to also account for the lack of a chronic study in the Database UF. Further, since it was noted that no new data were identified, it would be useful to more explicitly specify the methodology and rationale for assigning a 10x Database Deficiency UF, particularly since Table A6 in Appendix III does not include an option for full 10x Database Deficiency UF.

Total (Composite) UF

The composite UF is comprised or four areas of uncertainty of at least 10x each. The convention to collapse four areas of uncertainty to 3000x (despite mathematically amounting to 10000x at times) is based on four areas of 10x uncertainty (US EPA, 2002). As currently configured, the composite UF is 30,000x, which could be considered too uncertain to derive a RfD with confidence according to US EPA (2002) guidelines. Clarify and/or cite the methodology used the ascribe the total UF.

CalTOX Modeling

The previous 2006 PHR intake rate of 4 L_{eq}/day also considered incidental inhalation and dermal exposure. The new proposed intake rate, while also considering incidental inhalation and dermal exposure, estimated daily water intake to be 0.075 L_{eq}/kg-day (at the 95th%ile), which is 50% more than the previous rate (0.05 L_{eq}/kg-day if assuming an 80-kg adult based on the most recent Health and Nutrition Examination Survey (NHANES) survey data; US EPA, 2011b).

Recognizing that incidental inhalation or dermal exposure are not represented, the new proposed intake rate of 0.075 L_{eq}/kg-day is also more than twice the lifetime intake rate of 0.034 L/kg-day (at the 90th%ile) suggested by the most recent NHANES exposure data (US EPA, 2011b), which is also equivalent to an 80-kg adult drinking 2.4 L/day at the 90th%ile.

Thus, since CalTOX modelling suggests that incidental inhalation and dermal exposure and other life stages are contributing a significant portion to the estimated daily intake of 0.075 L_{eq}/kg-day, the updated model parameters and/or revised assumptions in the current model should be more transparent given that it is not a widely-recognized standard practice.

Relative Source Contribution (RSC)

A RSC of 80% was applied since drinking water sources are anticipated to be the primary source contributor for exposures, use of cis-1,2-DCE is less common today, and because cis-1,2-DCE is no longer in use and exposure to residues on food or inhalation exposures from ambient air are expected to be minimal. However, use of an 80% RSC represents a departure from a default (20%) factor and thus it is preferable to include a more empirical or semi-quantitative basis as support. Both cis- and trans-1,2-DCE are noted to be environmental degradation products of tricholoroethylene (TCE) and tetrachloroethylene (PCE), which have relatively more widespread exposure potential; to what extent TCE and/or PCE contribute to or can be considered additional source(s) of exposure to cis or trans-1,2-DCE is unclear.

For example, US EPA (2000) provides guidance to depart from the 20% default RSC. When considering the 80% ceiling RSC value, the Exposure Decision Tree (Figure 4-1) indicates that adequate exposure data be available "to describe central tendencies and high-ends for relevant exposure sources/ pathways" such that these data would enable "apportion" of the RfD into % contributions from each of the relevant exposure sources (e.g., food, water).

There is inadequate information to determine whether the proposed 80% RSC factor was derived using current practices or standard methodology or is supported by the available data because the methodology or empirical basis was not indicated. Attachment 2 of the September 20, 2017 OEHHA request indicated that "The RSC is the proportion of exposures to a chemical attributed to tap water, as part of total exposure from all sources (including food and air pollution)" which suggests at least a semi-empirical basis, but further details were not included.

It is also noted that OEHHA CalTOX modeling estimated tap water intake to be 0.075 L_{eq}/kg-day. Expressed as an apportion of the RfD, estimated exposure to cis-1,2-DCE at levels as high as 22 ppb in California public water systems is up to 136% of the proposed RfD of 0.00125 mg/kg-day according to: 0.022 mg/L (0.075 L_{eq}/kg-day) = 0.0017 mg/kg-day = 1.36 (0.00125 mg/kg-day). Thus, estimated drinking water exposure alone exceeds the proposed RfD without allowance for any other exposure source.

Risk Characterization

Ideally, this section would be more transparent with respect to the overall level of confidence, strengths and limitations, data gaps and/or remaining uncertainty that would inform future research. The very limited dataset did not allow for a mode of action or toxic moiety (including dose-dependency of these factors) to be proposed. The critical effect, increased relative kidney weight, was not associated with

renal histopathology or altered blood parameters suggestive of renal damage. The proposed PHG of 13 ppb is less than the 22 ppb detections in certain water supplies, but there is a large UF. Similarly, since exposure to cis-1,2-DCE at 22 ppb, assuming a modeled intake of 0.075 L_{eq}/kg-day, is in excess of the RfD, the CalTOX exposure assessment assumptions (e.g., 95th%ile) and uncertainties should be more explicit to aid in risk management decisions.

Comments Related to the "Big Picture"- Cis-1,2-DCE

In addition to the topics above, reviewers were asked to consider the following:

(a) For each PHG update, please comment on whether OEHHA has adequately addressed all important scientific issues relevant to each chemical and to the methods applied in deriving the PHG.

Response: As noted above, OEHHA has not provided adequate documentation of the basis, both in terms of derivation methodology and empirical evidence, for the 30x intraspecies UF or 80% RSC.

(b) For each chemical reviewed, please comment on whether a relevant study useful for assessing dose-response relationship or otherwise informing the PHG development was missed.

Response: The potentially useful studies appear to have been considered.

(c) PHGs must be protective of known sensitive subpopulations. Please comment on whether each PHG is health protective.

Response: The known sensitive subpopulation(s) have not been specified, thus precluding comment on whether the proposed PHG is protective of them.

Reviewer Comments for Trans-1,2-DCE

Benchmark Dose (BMD) Modeling

The BMD modeling for trans-1,2-DCE indicates that p>0.05 was considered acceptable. This is inconsistent with US EPA (2012) guidelines which specify that p>0.1 is acceptable. As the updated PHG document indicates that the BMR of 1 control standard deviation was elected to be consistent with EPA (2012) guidelines, it is unclear why there is a departure from EPA guidelines for the p value. Either be consistent with EPA guidelines or specify the rationale for deviating.

BMD modeling is also presumed to occur in the range of linear kinetics such that there is a monotonic dose-response. No indication is given as to whether the modeled dose ranges in the candidate studies (NTP, 2002, Shopp et al., 1985) are anticipated to be in the range of linear kinetics.

Many modelers also consider the margin (or ratio) between to the BMD_{10} and $BMDL_{10}$ to be an indicator of fit and confidence in the modeling results. The smaller the ratio, the better the fit in the dose range from which the $BMDL_{10}$ is extrapolated. The preference is for ratios < 2 (Muri *et al*., 2009). For trans-1,2-DCE, the BMD/BMDL ratio (77.22/14.5) of 5 suggest a nonoptimal fit, recognizing it is an acceptable fit according to US EPA (2012) guidelines. As a point-of-departure for the RfD, it may be preferable to use

the empirical NOAEL of 17 mg/kg-day for this response compared to the $BMDL_{10}$ of 14.5 mg/kg-day, which is a model estimate, recognizing that both values are approximately the same.

Consider expressing the point-of-departure, whether a rat NOAEL or $BMDL_{10}$, as a human equivalent dose (HED) according to current US EPA (2011a) guidelines. When inadequate toxicokinetic data are available to estimate human equivalent doses, US EPA (2011a) considers the default approach to be allometric scaling (BW ¾ power). US EPA (2012) BMD guidelines also recommend that the HED be estimated and that that BMDL values be expressed as HED.

Interspecies UF

The Introduction section notes that "the most current risk assessment practices and methods" were applied. US EPA (2011a) recommends expressing the point-of-departure as a human equivalent dose (HED) and adjusting the interspecies UF accordingly. If inadequate toxicokinetic data are available, US EPA (2001) considers the default approach to be allometric scaling (BW ¾ power) rather than using the animal point-of-departure. If the point-of-departure is expressed as a HED, the interspecies UF would be reduced from 10x to √10 to account for potential remaining interspecies toxicodynamic differences.

Intraspecies UF

Attachment 2 of the September 20, 2017 OEHHA request notes that "OEHHA is using standard peer-reviewed methodology to derive the PHG for cis-1,2-DCE" and the Introduction section of the PHG update notes that "the most current risk assessment practices and methods" were applied.

Use of a 30x intraspecies UF represents a departure from the default (10x) factor and should be accompanied by more explicit rationale and preferably, an empirical basis. There is more than one combination of toxicokinetic or toxicodynamic factors specified in Table A6 of Appendix III that could result in 30x and it is unclear which option(s) were elected and what data or rationale were used to support the option(s). For example, is 30x comprised of a 10x toxicokinetic factor and a √10 toxicodynamic factor, or vice-versa?

The stated rationale of "to account for sensitive individuals" is nondescript. Is this factor based on chemical-specific toxicokinetic or toxicodynamic data and derived based on current practices or recognized standard methodology, such as WHO/IPCS (2005) or US EPA (2014)? The methodology employed (e.g., 95%ile/median, the dose metric, the sensitive population) should be specified. Conversely, if the 30x factor is based on non-chemical-specific methodology and/or is not required to be empirically derived, this should be clarified in Appendix III. Either way, there is inadequate information to determine how the proposed factor of 30x was configured and whether it is supported by the available evidence because no data or rationale were indicated. Also, with respect to terminology, RfD are intended to account for sensitive "subpopulations" rather than sensitive "individuals".

Further, Appendix III notes that "when scientific evidence is compelling, these defaults are supplanted by alternative factors or modeling results". It is unclear and potentially misleading what the word "default" refers to in this statement as well as what the word "Default" in the title of Table A6 refers to, since there appears to be both default approaches as well as alternative factors being described in Table A6. What is the OEHHA definition of "default" and which scenarios in Table A6 are defaults and which are "alternative factors"? In practice or by convention, "default" tends to refer to both a magnitude (i.e.,

10x) and an approach (i.e., when there are no data). However, some of the approaches in Table A6 seem to be alternative (non-default) approaches, that do not require a chemical-specific and/or empirical basis and they can be applied in addition to (rather than supplant) default approaches. Thus, the criteria that constitute compelling scientific evidence is unclear, particularly in relation to when an alternative factor is adopted in addition to the default factor as well as when a default is supplanted by an alternative factor. There should also be a clearer distinction between science and policy.

Database Deficiency UF

The √10 factor for database deficiencies was noted to account for the lack of chronic or reproduction studies. The lack of a chronic study is already addressed with the 10x Subchonic Extrapolation UF and thus it is unconventional to also account for the lack of a chronic study in the Database UF.

Total (Composite) UF

The convention to collapse four areas of uncertainty to 3000x (despite mathematically amounting to 10000x at times) is based on four areas of 10x uncertainty (US EPA, 2002). As currently configured, the composite UF is 10000x, since an additional 3x intraspecies factor was applied to the default 10x. The current configuration does not equate to 3000x, and a 10000x UF could be considered too uncertain to derive a RfD with confidence according to US EPA (2002) guidelines. Clarify and/or cite the methodology used the ascribe the total UF.

CalTOX Modeling

The previous 2006 PHR intake rate of 4 L_{eq}/day also considered incidental inhalation and dermal exposure. The new proposed intake rate, while also considering incidental inhalation and dermal exposure, estimated daily water intake to be 0.075 L_{eq}/kg-day (at the 95th%ile), which is 50% more than the previous rate (0.05 L_{eq}/kg-day if assuming an 80-kg adult based on the most recent Health and Nutrition Examination Survey (NHANES) survey data; US EPA, 2011b).

Recognizing that incidental inhalation or dermal exposure are not represented, the new proposed intake rate of 0.075 L_{eq}/kg-day is also more than twice the lifetime intake rate of 0.034 L/kg-day (at the 90th%ile) suggested by the most recent NHANES exposure data (US EPA, 2011b), which is also equivalent to an 80-kg adult drinking 2.4 L/day at the 90th%ile.

Thus, since CalTOX modelling suggests that incidental inhalation and dermal exposure and other life stages are contributing a significant portion to the estimated daily intake of 0.075 L_{eq}/kg-day, the updated model parameters and/or revised assumptions in the current model should be more transparent given that it is not a widely-recognized standard practice.

Relative Source Contribution (RSC)

A RSC of 80% was applied for trans-1,2-DCE since drinking water sources are anticipated to be the primary source contributor for exposures and US EPA's TRI data indicating that California has had few releases of trans-1,2-DCE and it is not heavily used in California, therefore exposure to residues on food and through inhalation from ambient air are expected to be minimal. However, use of an 80% RSC

represents a departure from a default (20%) factor and thus it is preferable to include a more empirical or semi-quantitative basis as support. Both cis- and trans-1,2-DCE are noted to be environmental degradation products of tricholoroethylene (TCE) and tetrachloroethylene (PCE), which have relatively more widespread exposure potential; to what extent TCE and/or PCE contribute to or can be considered additional source(s) of exposure to cis or trans-1,2-DCE is unclear.

For example, US EPA (2000) provides guidance to depart from the 20% default RSC. When considering the 80% ceiling RSC value, the Exposure Decision Tree (Figure 4-1) indicates that adequate exposure data be available "to describe central tendencies and high-ends for relevant exposure sources/ pathways" such that these data would enable "apportion" of the RfD into % contributions from each of the relevant exposure sources (e.g., food, water).

There is inadequate information to determine whether the proposed 80% RSC factor was derived using current practices or standard methodology or is supported by the available data because the methodology or empirical basis was not indicated. Attachment 2 of the September 20, 2017 OEHHA request indicated that "The RSC is the proportion of exposures to a chemical attributed to tap water, as part of total exposure from all sources (including food and air pollution)" which suggests at least a semi-empirical basis, but further details were not included.

Risk Characterization

Ideally, this section would be more transparent with respect to the overall level of confidence, strengths and limitations, model assumptions, data gaps and/or remaining uncertainty that would inform future research.

The BMD approach (i.e., a model) is noted as being "more sophisticated" than the NOAEL, but may not necessarily result in greater accuracy or confidence.

Comments Related to the "Big Picture"- Trans-1,2-DCE

In addition to the topics above, reviewers were asked to consider the following:

(a) For each PHG update, please comment on whether OEHHA has adequately addressed all important scientific issues relevant to each chemical and to the methods applied in deriving the PHG.

Response: As noted above, it may be preferable to use the empirical NOAEL of 17 mg/kg-day for the point-of-departure compared to the $BMDL_{10}$ of 14.5 mg/kg-day, which is a model estimate, recognizing that both values are approximately the same. Also noted above, OEHHA has not provided adequate documentation of the basis, both in terms of derivation methodology and empirical evidence, for the 30x intraspecies UF or 80% RSC.

(b) For each chemical reviewed, please comment on whether a relevant study useful for assessing dose-response relationship or otherwise informing the PHG development was missed.

Response: The potentially useful studies appear to have been considered.

(c) PHGs must be protective of known sensitive subpopulations. Please comment on whether each PHG is health protective.

Response: The known sensitive subpopulation(s) have not been specified, thus precluding comment on whether the proposed PHG is protective of them.

References

Muri, S. D., Schlatter, J. R., and Brüschweiler, B. J. (2009). The benchmark dose approach in food risk assessment: Is it applicable and worthwhile? Food Chem. Toxicol. 47, 2906-2925.

U.S. EPA (U.S. Environmental Protection Agency). 2000. Methodology for deriving ambient water quality criteria for the protection of human health. Office of Water, EPA-822-B-00-004, October 2000. Available from: http://www.nj.gov/drbc/library/documents/EPA_human-health-criteria2000.pdf

U.S. EPA (U.S. Environmental Protection Agency). 2002. A Review of the Reference Dose and Reference Concentration Process. EPA/630/P-02/002F. 01 Dec 2002. U.S. EPA, Risk Assessment Forum, Washington, DC. Available from: http://www.epa.gov/raf/publications/pdfs/rfd-final.pdf.

U.S. EPA (Environmental Protection Agency). 2011a. Recommended Use of Body Weight ¾ as the Default Method in Derivation of the Oral Reference Dose. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, EPA/100/R11/0001. Available from: http://www.epa.gov/raf/publications/interspecies-extrapolation.htm.

U.S. EPA (Environmental Protection Agency). 2011b. Exposure Factors Handbook: 2011 Edition. EPA-600-R-09-052F. U.S. Environmental Protection Agency, Office of Research and Development, Washington, DC. Available from: http://www.epa.gov/ncea/efh/pdfs/efhcomplete.pdf.

U.S. EPA (U.S. Environmental Protection Agency). 2012. Benchmark Dose Technical Guidance. Risk Assessment Forum. EPA/100/R-12/001. June 2012. Available from: http://www.epa.gov/raf/publications/benchmarkdose.htm.

US EPA (U.S. Environmental Protection Agency). 2014. Guidance for applying quantitative data to develop data-derived extrapolation factors for interspecies and intraspecies extrapolation. Risk Assessment Forum. EPA/100/R-14/002F. Washington (DC) 20460. Available from: https://www.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf

WHO/IPCS (World Health Organization/International Programme on Chemical Safety). 2005. Chemical-Specific Adjustment Factors (CSAF) for interspecies differences and human variability: guidance document for the use of data in dose/concentration-response assessment. (IPCS harmonization project document no. 2). WHO/IPCS/01.4, 1-96. Geneva, Switzerland. Available from: http://www.inchem.org/documents/harmproj/harmproj/harmproj2.pdf