Responses to Comments

Technical Support Document: Public Health Goal for 1,2-Dibromo-3-Chloropropane in Drinking Water

July 2020

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Responses to Comments on Technical Support Document: Public Health Goal for 1,2-Dibromo-3-Chloropropane in Drinking Water

Prepared by

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
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INTRODUCTION

This document contains responses to comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for 1,2-dibromo-3-chloropropane (DBCP).

OEHHA released the first draft of this PHG document for public comment on March 29, 2019, and held a public workshop on May 13, 2019 in Sacramento, California. The public comment period closed on May 13, 2019 and OEHHA received no comments.

Pursuant to Health and Safety Code section 116365(c)(3)(D), OEHHA submitted the draft DBCP PHG document for peer review following the closure of the first comment period. Comments were received from the peer reviewers in October 2019.

OEHHA evaluated comments from external scientific peer reviewers and revised the technical support document as appropriate. The second draft of the PHG technical support document was released for public comment on May 29, 2020. The public comment period closed on June 29, 2020 and OEHHA received no comments.

The external scientific peer reviewers were:

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The full peer review comment letters are posted on the OEHHA website along with this response document, and the final version of the DBCP PHG document.

In this document, comments appear in italics where they are directly quoted from the submission.

For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA web site at www.oehha.ca.gov.

OEHHA may also be contacted at:

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RESPONSES TO EXTERNAL SCIENTIFIC PEER REVIEW COMMENTS

RESPONSES TO COMMENTS RECEIVED FROM DR. DAVID PHILLIPS

Comment 1: *The primary adverse health concern associated with human exposure to DBCP is cancer. I consider that in the proposed PHG for DBCP based on cancer, the OEHHA has adequately addressed all relevant scientific issues. The current analysis has considered both oral exposure and exposure by inhalation. Also included in the risk assessment are adequate safety factors to take into consideration interspecies extrapolation (pharmacodynamics and pharmacokinetics) as well as intraspecies variability (sensitive and potentially vulnerable subgroups, including infants and children) in the human population. While I have not reviewed the evidence of reproductive toxicity nor the calculations for its risk assessment, I note that the health-protective concentration arrived at for noncancer effects of DBCP is 0.2 ppb, which is considerably higher than the PHG for DBCP of 0.02 ppb based on an estimated lifetime cancer risk of 1 in one million. Therefore, adoption of the latter value for cancer risk would provide adequate protection against potential adverse reproductive health effects.*

Reponse 1: OEHHA acknowledges the comment.

Comment 2: *In my opinion, the proposed updated PHG for DBCP of 0.002 ppb based on a lifetime cancer risk of 1 in one million, very similar to the 1999 value of 0.0017 ppb, has been arrived at from appropriate consideration and analysis of the scientific evidence on the carcinogenic activity and mode/mechanism of action of DBCP.*

Response 2: OEHHA acknowledges the comment.

RESPONSES TO COMMENTS RECEIVED FROM DR. KAN SHAO

Comment 1: *Tumor incidences in rats and mice administered DBCP in the diet for 104 and 78 weeks presented in Table 4 were used to estimate the oral cancer slope factor. ... A number of critical issues have been identified: The last sentence on Page 2 (in the section of "Point of Departure") states, "the BMR is typically set at 5% above the background or the response of the control group for dichotomous data". However, no reference was cited to support the claim. Actually, EPA's Benchmark Dose Technical Guidance (2012) suggests that 10% extra risk should be used as a default choice for standard reporting.*

Response 1: It is OEHHA's current policy to use a benchmark response (BMR) of 5% extra risk for dichotomous data and this has been done in several externally peer reviewed PHGs.

Comment 2: *Additionally, the document should clearly mention in the main text that the BMD calculated for dichotomous data in this report is based on the definition of extra risk rather than added risk (even though extra risk is the default choice).*

Response 2: The main text has been revised to reflect the use of "the BMDS Multistage-Cancer model with a BMR of 5% extra risk."

Comment 3: *Using BMR=5% may not necessarily result in a more health-protective (i.e., conservative) cancer slope factor. The data shown in Figure A3 were used to recalculate the cancer* [slope factor] *based on BMR=10%, and a CSF of 0.137523 was obtained (it's 0.114477 if BMR=5% as reported in Appendix I).*

Response 3: It is OEHHA's policy to use a BMR of 5% for cancer analyses, which has been found to be sufficiently health-protective. Because the slope factor is based on linear extrapolation in the low dose region, values derived by using BMR 5% or 10% should be relatively close . For example, running a multisite analysis on the male rat data used to derive the oral cancer slope factor (CSF) (Draft Table 4) with a 10% BMR gives a multisite CSF_{animal} of 0.30 $(mg/kg\text{-}day)^{-1}$ versus the CSF_{animal} of 0.29 $(mg/kg\text{-}day)^{-1}$ using a BMR of 5% (Draft Table 5).

Comment 4: *The data shown in Figure A4 (as well as the male mice and female mice data listed in Table 4) are not appropriate for BMD modeling. As suggested in EPA's Benchmark Dose Technical Guidance (2012), the minimum requirement for a data set for BMD modeling is three dose levels (control and two additional dose levels). A data set with only the control and one exposure dose level cannot provide enough information to inform the shape of the dose-response relationship and will introduce substantial uncertainty into BMD estimation.*

Response 4: This analysis has been removed from the draft and instead, the data for male rats were used to derive an oral CSF. Despite a seven-fold lower CSF, as compared to the 1999 PHG, OEHHA agrees that the more complete dataset should be used.

Comment 5: *(1) The endpoint presented in Table 2 and modeled is the percent abnormal spermatozoa in rabbits, which should be a non-negative value. However, the assumption of the distribution of continuous endpoint (i.e., the percent) used in EPA's BMDS is normal distribution. Consequently, the fitted results shown in Figure A1 have relative large confidence intervals stretching into negative region on the y-coordinate, which is biologically implausible. (2) The BMD was defined as the dose level that caused one standard deviation (of the control group) shift in the mean response. However, because of the very limited number of animals in the control group (e.g., 2 in*

the dataset shown in Table 2) and the way to model with-in dose group variance in this analysis (i.e., modeled as a non-constant dose-dependent variance), it is neither an appropriate nor reliable way to define the BMD based on the estimated SD of the control group.

Response 5: OEHHA acknowledges the comments and has removed the Rao (1982) abnormal spermatozoa with no recovery period data (Draft Table 2) and the BMD modeling results from the PHG. The noncancer endpoint is based on the no-observed-adverse-effect level (NOAEL) from the Rao et al. (1982) study in the updated PHG draft.

Comment 6: *Although the data presented in Table 3 have a* [s]*lightly larger sample size in the control group (than the dataset in Table 2), it is still not appropriate to define the BMD based on one SD shift. The main reason is that modeling the with-in dose group variance as a dose-dependent variable (i.e., would increase as dose increases in this case) could be affected by the variances in all dose groups, and the overall sample size of the dataset in Table 3 is still highly limited.*

Response 6: Benchmark dose modeling is OEHHA's preferred approach for dose-response analysis when data are amenable to modeling. A brief discussion regarding the limitations of this data set was added, and clarification around the use of the NOAEL as the point of departure (POD) was included.

Comment 7: *Suggestions on BMD analysis for non-cancer effects: (1) Employing the lognormal distribution assumption for the endpoint of percent abnormal spermatozoa to avoid the potential negative values modeled in the BMDS. The PROAST software published by RIVM (Slob 2002) and the Bayesian Benchmark Dose modeling system (BBMD) (Shao and Shapiro, 2018) both used the lognormal distribution as the default modeling option and can be used for analyzing these two data sets.*

Response 7: OEHHA is no longer modeling the data set to which this comment is referring (see Response 5).

Comment 8: *Suggestions on BMD analysis for non-cancer effects: (2) Due to the very limited sample size in the two data sets, it is not reliable to model the* [within] *dose group variance, and consequently it is not appropriate to define BMD based on one SD shift. So, a more proper way to define BMD is to use 5% change in the modeled central tendency of response.*

Response 8: The NOAEL of 0.1 parts per million (ppm) used in the 1999 PHG is retained as the noncancer POD. However, BMD analysis provides support for the value derived using the NOAEL approach. For continuous data, a BMR of one standard

deviation (1 SD) from the control mean is typically used when there are no data to indicate what level of response is biologically significant (US EPA, 2012). Draft Table 2 and the analysis of that data were removed from the PHG document due to lack of statistical significance and poor model fit. For the data shown in Draft Table 3, benchmark dose modeling was performed using both 5% and 10% relative deviation for comparison, yielding BMDL values of up to 10-fold lower than that derived using one standard deviation. In the absence of a quantitative measure of the level of adversity of the ultrastructural aberration in late spermatids, the $BMDL_{1SD}$ (0.08 ppm) from the Rao et al. (1982) study appears to support the NOAEL of 0.1 ppm from the same study that is selected as the POD for deriving the health-protective concentration for DBCP.

Comment 9: *On page 16 of the main report, "Tumor incidence rates for both rats and mice are much higher than the BMR of 5%, thus CSFs are not estimated for these studies." The data presented in Tables 6 and 7 are not appropriate for BMD modeling mainly because the data lack adequate dose-response information due to relatively high doses used in the study design, but not because the response rates in the exposure dose groups were much higher than 5%.*

Response 9: The text on page 16 has been modified to clarify that modeling was not performed due to a lack of adequate dose-response information for lower dose ranges.

Comment 10: *On page 18 of the main report, the explanation on how the BMDL was calculated: it seems that the unit on the left side of the equal sign should be "mg/kg-day" instead of "ppm".*

Response 10: The units on page 18 have been corrected.

Comment 11: *On page 11 of the main report, "OEHHA's current dose-response analysis with benchmark dose software (BMDS version 2.5, US EPA) demonstrates that these data can be modeled". Whether the data can be modeled by the BMDS software should not be used as a justification for appropriateness of modeling the data for BMD analysis.*

Response 11: OEHHA's current methodology for developing PHGs includes preferentially using benchmark dose modeling to derive PODs, as described in the methodology section of this document. The statement referenced above is not a justification for modeling, but instead an observation that the data are amenable to modeling.

Comment 12: *On page 26 of Appendix I in the first paragraph, the report listed four selection criteria. It is better to list the criteria in the order of how they are used, so it should be: goodness of fit p-value ≥ 0.05; scaled residual ≤ the absolute value of two; visual inspection of the dose-response curve; and the Akaike's information criterion (AIC).*

Response 12: The order of criteria listed has been adjusted to follow the order shown in Table A1.

Comment 13: *On page 26 of Appendix I in the first paragraph, the document mentioned that the p- value ≥ 0.05 was used as one of the criteria for goodness of fit. However, the EPA's Benchmark Dose Technical Guidance (2012) suggests using p-value ≥ 0.1 to evaluate goodness of fit. It's better to provide justification in the document for using p-value ≥ 0.05 as the criterion.*

Response 13: OEHHA's risk assessment guidelines (OEHHA, 2008) consider a goodness-of-fit p-value ≥ 0.05 to be acceptable. These guidelines were peer-reviewed and approved by the state's Scientific Review Panel on Toxic Air Contaminants, which consists of independent scientific experts. US EPA's Benchmark Dose Technical Guidance Document (2012) indicates that a p-value <0.1 may not necessarily indicate a poor-fit model. Additional criteria may be used to determine a model's fit, including variability in the endpoint, the visual fit of the model, and the scaled residuals for data points in the low dose range. It is OEHHA's policy to thoroughly review all models, including those with a p-value < 0.1 but ≥ 0.05. A footnote was added to Appendix I to clarify the use of p-value ≥ 0.05.

Comment 14: *On page 26 of Appendix I in Table A1, the "scaled residual" should be listed under the column name "Goodness of Fit", and the "AIC" column should be parallel to "Goodness of Fit". AIC values are mainly used to compare different models not only based on how well the model fit the data but also punish the models with more parameters. "P-value" and "scaled residual" are the two criteria to evaluate goodness of fit.*

Response 14: The term "Goodness of Fit" was removed from Table A1.

Comment 15: *On page 3 of the main report, references should be cited for paragraph discussing the limitations of the NOAEL/LOAEL approach.*

Response 15: Reference to Davis et al. (2011) was added.

Comment 16: *The studies reviewed in the draft document are adequate, and no additional studies are identified.*

Response 16: OEHHA acknowledges the comment.

Comment 17: *The BMD modeling strategies recommended (e.g., defining BMD based on the change of central tendency of response for noncancer endpoints, and trying BMR = 10% for cancer endpoint) above may produce* [a] *more protective PHG. Whether the newly proposed PHG is health protective can be better addressed when additional analyses are completed.*

Response 17: BMD modeling is no longer being used for noncancer POD derivation, and derivation of the oral CSF using a BMR of 10% results in essentially the same value derived using a BMR of 5% (see Response 3).

RESPONSES TO COMMENTS RECEIVED FROM DR. MARVIN MEISTRICH

Comment 1: *After reviewing the literature on DBCP since the publication of the PHG in 1999, OEHHA concludes that male reproductive toxicity remains the primary and most sensitive noncancer effect associated with human exposure to this chemical: AGREE.*

Response 1: OEHHA acknowledges the comment.

Comment 2: [The PHG] *appears to be protective based on what is known, but better animal model studies are needed to clarify the reproductive effects on fetal and early pubertal stages.*

Response 2: OEHHA acknowledges the comment.

Comment 3: *This document presents the data selected on cancer induction and reproductive toxicity of DBCP. No other information is presented on non-cancer effects but I am in agreement that reproductive toxicity represents the most sensitive non-cancer adverse endpoint and should be used for the non-cancer MCL and PHG guidelines.*

Response 3: OEHHA acknowledges the comment.

Comment 4: *One major change from the 1999 guidelines in calculating the updated PHG involves the use of the Benchmark Dose (BMD) instead of the NOAEL for*

calculating the Point of Departure for setting the regulatory limits. While the BMD approach does indeed have advantages over using the NOAEL, as clearly stated on page 3, the use of the BMD approach for the reproductive risk here has many flaws, and is actually inferior to using the NOAEL.

Response 4: OEHHA acknowledges there are limitations in modeling data for the single endpoint of abnormal spermatozoa in the Rao et al. (1982) study. The draft PHG has been revised to note these limitations and to use the NOAEL, based on multiple testicular effects, as the noncancer POD.

Comment 5: *A detailed discussion of age-specific DBCP exposure and age sensitivity factors (ASFs) for cancer risk is given. Although there are only limited data on ASFs for reproductive risks, the indications of greater sensitivity of fetal (Warren et al. Biol. Reprod. 1988), neonatal (Liu et al. Toxicol. Appl. Pharm., 1987), and early pubertal rats (Sod-Moriah et al. Andrologia, 1990) to testicular damage from DBCP should be referenced and considered.*

Response 5: OEHHA added a statement on increased sensitivity to testicular damage during development, including references listed by the reviewer. Increased sensitivity during development is accounted for in the intraspecies uncertainty factor (see Response 14.

Comment 6: *This reviewer agrees that the study by Rao et al. (1982) on the effects of 14-week exposure to DBCP by inhalation is an excellent study for evaluation of reproductive toxicity; however, a study by Foote et al. (1986), which administered DBCP for 10 weeks in the drinking water, should also be considered in the analysis. Although the latter study is in the reference list, it is not mentioned in the text.*

Response 6: OEHHA has added data and analysis for the Foote et al. (1986) study to the noncancer section of the draft PHG, and added a discussion comparing this study to the Rao et al. (1982) study. Benchmark dose modeling results for Foote et al. (1986) were added to Appendix I.

Comment 7: *In the section marked "Toxicological Review", the most of the more recent literature does not add significantly to improving the calculations of MCL and PHG levels for non-cancer adverse effects. The paper by Foote (2002) involved exposure in vitro which cannot be related to in vivo exposure levels. Also the statement that the DBCP-exposed human sperm were unable to penetrate zona-free hamster oocytes may be misleading, as this result was not reported as being significantly different from controls. The results of Yoshida et al. (1998) were questionable because of the poor histology and the RT-PCR did not seem to have loading controls. The*

relevant factor from the study of Meistrich et al. (2003) was the persistence of the effect from a short treatment. However, the question of whether there are unique aspects of the rat model and its relevance to human is still open to discussion. The papers on the genotoxicity of DBCP are probably more relevant to its carcinogenicity than the reproductive effects. The only relevant observation to genetic effects directly related to reproduction is the observation by Rao et al (Fund. Appl. Tox. 1983) that inhalation exposure of male rats to DBCP at 10 ppm resulted in increased post-implantation embryonic loss (dominant lethal mutations). The most important study in this section was that of Slutsky et al (1999), which provided excellent support the widespread adverse effects of DBCP exposure on human spermatogenesis and the persistence of the effect.

Response 7: OEHHA acknowledges the comment.

Comment 8: *The change from use of the NOAEL for multiple endpoints regarding spermatogenesis to the use of BM*[D]*S modeling for the single endpoint of abnormal "spermatozoa" (Tables 2 & 3) is open to multiple criticisms…and is not justified. The terminology is incorrect. Testicular sections were analyzed and the cells evaluated were late spermatids in various stages of development. These cells are considered to be spermatozoa only after release from the seminiferous epithelium of the testis.*

Response 8: OEHHA used the terminology presented by the study authors when discussing the results from the Rao et al. (1982) study.

Comment 9: *Method for choosing the sample for evaluation of these abnormalities is inadequately explained in Rao et al. (1982). No mention is made how many sections were evaluated, how many tubules were evaluated in each section, and how many cells were evaluated in each tubule. The authors did not consider that each tubule could have been in a different stage of the cycle of the seminiferous epithelium. So no effort was made to match stages in the different dose groups. The sensitivity of identifying abnormalities could be dependent on the stage of maturation of the spermatids. It is not demonstrated that the different treatment groups were evaluated using comparable stages.*

Response 9: A discussion of the study limitations was added, including the possible discrepancies in seminiferous epithelium cycles between samples.

Comment 10: *Ultrastructural aberration in late spermatids is not an assay for reproductive toxicity that has been used in any other study that this reviewer is aware of. So the level of consequence of how much of an adverse effect this is, has not been evaluated. The use of the criterion of the BMR (benchmark response) being one SD*

from the control mean is extremely weak. The control mean of the data immediately after exposure is based on results with 2 animals. Thus the standard deviation, calculated from these 2 values, is an extremely poor estimate of the true standard deviation of the data for % abnormal "spermatozoa"… The data on % abnormal "spermatozoa" immediately after exposure does not show any significant difference between treatment groups by ANOVA (acknowledged in the Draft Report). Furthermore, linear regression analysis does not show that the slope of the dose response curve is not significantly greater than zero. Although I did not follow all the statistical analysis of the BMD calculations, these factors suggest calculation of a BMD, when there is no significant dose response, is not meaningful.

Response 10: OEHHA chose the Rao et al. (1982) study as the basis for the noncancer endpoint because it is the most sensitive study deemed to be of sufficient quality. The PHG draft has been updated to reflect a NOAEL of 0.1 ppm as the noncancer POD, based on multiple testicular effects observed in this study. The data set and analysis referred to by the reviewer (Draft Table 2), including the benchmark dose modeling results, have been removed from the draft document.

Comment 11: *There does not seem to be any biological basis for the observation that the % abnormal spermatozoa is higher after 32 weeks recovery, when sperm count and viability have recovered to control levels. This reviewer suggests that the increased % abnormal "spermatozoa" may be a result of the failure of the assay to match the stages of late spermatids in different groups, and not an actual increase.*

Response 11: A brief description of this uncertainty within the study results was added to the text.

Comment 12: *The justification for choosing the linear model for the BMD for the 32-week recovery period, that* [it] *produces a more health protective BMDL* [than] *the* [Exponential Model 2]*, although it has a lower AIC value, is not justified. The additional cost of the lower BMDL needs to be considered. In summary, this is another example, which this reviewer has seen before in other USEPA reviews, of forcing the BMD methods to model a weak endpoint. There are stronger endpoints, for which the NOAEL can be used, such as sperm count and viability, but perhaps the data on these do not meet the criteria for using BMD modeling. This reviewer strongly recommends remaining with the use of the NOAEL of 0.1 ppm rather that attempting this flawed calculation of BMD.*

Response 12: OEHHA has revised the draft PHG to reflect the use of the NOAEL of 0.1 ppm, based on multiple testicular effects, as the POD for noncancer effects.

Comment 13: *As mentioned above, the data of Foote et al. (1986) may be appropriate for independently obtaining NOAEL or BMD values for the reproductive toxicity of DBCP in the rabbit model, for comparison with the results from Rao et al. (1982). The advantage of the Foote study, is that the DBCP was administered in the drinking water, which is which is currently the major route of human exposure. The use of the Foote data eliminates the uncertainties in calculating the uptake from inhalation from the Rao data. … No attempt is made to determine the uptake (m3/day inhaled for a given sized rabbit, % absorption) in rabbits. Then the calculations are pursued using humans exposed to the same air concentrations. There is an underlying unsubstantiated assumption that humans have the same daily uptake per kg of this contaminant in the air as do rabbits. Thus it seems more appropriate to use data based on ingestion. ... Based on 0.58 mg/kg/day as the POD, the ADD would be 0.58 µg/kg/day, and the PHG concentration would be 0.08 µg/L, which is 40% of the value obtained from the inhalation data of Rao. It is possible that the extrapolation of ingestion results might have lower uncertainty factor than the extrapolation of inhalation results. It also may be possible to use BMD modeling of the Foote data.*

Response 13: The data from Foote et al. (1986) were added to the draft document, along with a discussion and full analysis of the study. The benchmark dose modeling results were added to Appendix I. OEHHA determined a NOAEL of 0.67 milligrams per kilogram of body weight per day (mg/kg-day) and a $BMDL_{1SD}$ of 0.55 mg/kg-day from Foote et al. (1986). Based on calculations performed in the 1999 DBCP PHG technical support document, the NOAEL of 0.1 ppm from Rao et al. (1982) is equivalent to 0.044 mg/kg-day, assuming 50% absorption via the inhalation route. A comparison of PODs between the Foote et al. (1986) and Rao et al. (1982) studies shows that the NOAEL of 0.1 ppm from the Rao et al. (1982) study is more health-protective.

Comment 14: *Although the Uncertainty Factor (UF) of 1,000 used here is the same as in the 1999 guidelines, the factors used in calculating it have changed. A more clear justification of those changes would strengthen the presentation of the guidelines. In the 1999 guidelines, the 1,000-fold UF was based on 10-fold for interspecies extrapolation, 10-fold for subchronic-to-chronic extrapolation, and 10 to account for variability among individuals. The currently proposed guidelines also use a UF of 1,000 but it is based on 10 for interspecies extrapolation, 30 for intraspecies variability, and 3.2 for database uncertainty around irreversibility of testicular effects and need for larger studies. The reasons for deletion of the subchronic-to-chronic UF are presented on page 19. The choice of 30 for intraspecies variability is mentioned on page 3, to account for some sensitive populations. Indeed there is evidence that the testes of fetal and pubertal stage animals might be more sensitive to DBCP than adult testes, but it is not clear what new information was obtained since 1999 to warrant the change of the UF from 10 to 30 for intraspecies variability.*

Response 14: OEHHA's current default intraspecies UF is 30. The previous PHG was released in 1999, prior to OEHHA's development of a technical support document for noncancer risk assessment, which included an updated set of default uncertainty factors (OEHHA, 2008). This document, cited in the *Uncertainty and Variability Factors* section on page 3, details case studies and OEHHA's analyses that found a value higher than √10 should be considered for the pharmacokinetic component of the intraspecies UF. Thus, the default intraspecies UF was raised to 30.

REFERENCES

OEHHA (2008). Air Toxics Hot Spots Risk Assessment Guidelines: Technical Support Document for the Derivation of Noncancer Reference Exposure Levels. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA. http://www.oehha.ca.gov/air/hot_spots/2008/NoncancerTSD_final.pdf.

OEHHA (2009). Technical support document for cancer potency factors: methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA. https://oehha.ca.gov/air/crnr/technical-support-document-cancer-potency-factors-2009.