Public Health Goals

Responses to Peer Review and Major Public Comments on Technical Support Document

Public Health Goals for Carbofuran, Diquat, Endrin, Picloram, and Thiobencarb in Drinking Water

September 2016

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

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Carbofuran

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in Drinking Water

Prepared by

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

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INTRODUCTION

This document contains responses to peer review and major public comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for carbofuran, diquat, endrin, picloram, and thiobencarb.

OEHHA released the first draft of this PHG document for public comment on August 14, 2015. The public comment period closed on September 28, 2015. OEHHA received one comment from the Sacramento River Source Water Protection Program.

Health and Safety Code Section 116365(c)(3)(D) requires the first draft of PHG documents to undergo external scientific peer review using the process set forth in Health and Safety Code Section 57004. The University of California, pursuant to its interagency agreement with CalEPA regarding external scientific peer review of documents produced by CalEPA programs, identified the three peer reviewers of the draft document. OEHHA received the peer review comments in January 2016.

The three peer reviewers were:

- James E. Klaunig, PhD., Professor, School of Public and Environmental Affairs, Indiana University at Bloomington
- Jennifer Seed, Ph.D., Risk Assessment Consultant, Alexandria, VA
- David Stone, Ph.D., Associate Professor, Department of Environmental and Molecular Toxicology; Director, National Pesticide Information Center, Oregon State University

OEHHA released the second draft of this PHGs document for public comment on July 29, 2016. The public comment period closed on August 29, 2016 and no comments were received.

Changes have been made in response to comments received, and have been incorporated into the final version of the PHG document posted on the OEHHA web site. For the sake of brevity, the more important or representative comments were selected for responses. Comments appear in quotation marks 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 MAJOR COMMENTS RECEIVED FROM UNIVERSITY OF CALIFORNIA PEER REVIEWERS (JANUARY 2016)

Comments from James E. Klaunig (Indiana University)

CARBOFURAN

Comment 1: "One concern regarding the use of the Pant et al 1995 study is the lack of the inclusion of the body weight data in Table 3…. These data should be included in the table since a decrease in body weight may have an effect on organ weights…"

Response 1: This point is well taken. However, body weight data in the Pant et al. (1995) publication were presented as a graph only and not reported as numerical values. OEHHA did use the graph to estimate the difference between the dosed groups and the controls. However, due to the uncertainty in these estimates, no statistical analysis was performed. This information has been added to the text of the PHG document.

Furthermore, absolute organ weights were used as the health endpoint instead of relative organ weights because reproductive organ weight is not necessarily related to body weight changes.

Comment 2: **"**The draft document notes that 'Absolute organ weights were analyzed instead of relative organ to body weight ratio as reproductive organ weight is not necessarily related to body weight changes' (page 17). This comment should be referenced since it is essential to the establishing the decrease in testes weight as an important endpoint."

Response 2: OEHHA agrees. A reference has been added.

DIQUAT

Comment 1: "The low spontaneous incidence of cataracts should be amplified in the report. A search of the literature by this reviewer, confirmed that the incidence of cataracts in the rat are very low. A citation in the report on the low incidence should be included (Taradach, C., B. Regnier, and J. Perraud. 'Eye lesions in Sprague-Dawley rats: type and incidence in relation to age.' Laboratory animals 15.3 (1981): 285-287.)"

Response 1: The suggested citation has been added to the PHG update to support the identification of cataracts as the critical endpoint.

Comment 2: "The linkage of Diquat exposure to Parkinson's disease requires modification. While there are a number of reports suggesting a linkage between parquet and other herbicides and neurodegeneration, the findings are confounded by mixtures of compounds, lack of proper dose and administration approaches (Miller, Gary Wright. 'Paraquat: the red herring of Parkinson's disease research.' *Toxicological Sciences* 100.1 (2007): 1-2.)."

Response 2: This comment is supported by the reference provided and the text has been modified to include the uncertainty regarding the link between paraquat and Parkinson's disease.

ENDRIN

Comment 1: "I have several concerns over the use of this study. One is that fact that the study was not published in peer review literature. It is a report from the a lab at the University of Cincinnati to Velsicol chemical Company *Jolley, W. P., et al. 'Effects exerted upon beagle dogs during a period of two years by the introduction of 1, 2, 3, 4, 10, 10-hexachloro-6, 7, 10 epoxy-1, 4, 4a, 5, 6, 7, 8, 8a-octahydro-1, 4-endo, endo 5, 8-dimethanonaphtha into their diets.' Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, OH. Report to Velsicol Chemical Corporation (1969).)."*

Response 1: In developing PHGs, OEHHA uses primary sources of data. This includes published peer-reviewed studies as well as studies performed for chemical companies that, for proprietary reasons, are not published in the peer-reviewed literature. The Jolley et al. (1969) study falls under the latter category. For pesticides, such studies are often submitted to US EPA for registration purposes and are performed under specific guidelines. No new animal toxicity studies for endrin have been published since the release of the original PHG in 1999 and the update in 2008; thus OEHHA concludes it is appropriate to retain the Jolley et al. (1969) study as the critical study for PHG derivation. This is consistent with US EPA's and the Agency for Toxics Substances and Disease Registry's use of the same study to develop a chronic oral reference dose and a chronic oral minimum risk level, respectively, for endrin.

Comment 2: "…it is unclear how many dogs were treated with endrin. The table in the draft document (Table 8) reports only on the number of dogs examined, not the number of dogs treated."

Response 2: This was described in the PHG document as follows: "… three beagle dogs/sex/dose were fed endrin at 0, 0.1, 0.5, 1.0, 2.0, or 4.0 ppm in the diet for two years (Jolley et al., 1969). Additional groups of four dogs/sex/dose were fed 0, 1.0, or 4.0 ppm endrin in the diet. Two dogs of each sex from the 0, 1.0, and 4.0 ppm groups were sacrificed at six and twelve months."

Comment 3: "Also the liver effects noted in the draft document (pigmentation and vacuolation are poorly defined terms. Pathological results for this study should be reported and summarized in the draft document. Vacuolation could represent a number of changes in the liver including fatty change, glycogen deposition and or necrosis. Pigmentation could be in hepatocytes or in Kupffer cells. Pigmentation could be iron deposition from RBC or the result of autophagic events in the cells. These concerns should be addressed in the draft document."

Response 3: The terms used by OEHHA were those provided in the study report. The study report also stated, "The Kupffer's cells were of usual appearance in all livers." Thus, no findings were noted for Kupffer's cells in the PHG document. Since the study report did not provide more details on the appearance of the vacuoles or pigmentation, OEHHA cannot provide statements regarding the cause of the changes observed in hepatic cells.

PICLORAM

Comment 1: "The use of absolute liver weights in setting the PHG (from the Dow 1982 study) needs further explanation and discussion."

Response 1: The proposed PHG is based on relative liver weights (see Table 14 of the document).

Comment 2: "Additionally, the rat study cited as Dow (Dow, 1986) is not cited in the references for this compound. The only reason for dismissing this study (Dow 1986) was noted as 'This rat study is not chosen as the critical study because the POD would be higher than that derived from the Dow (1982) study, thus OEHHA is retaining the Dow (1982) study as the critical study for PHG derivation' (page 44). More justification should be provided as to why the Dow 1986 was not considered."

Response 2: The citation was added to the draft. The dog and the rat studies had similar dose range and the same route of exposure. Both studies showed liver is the target organ but dogs were more sensitive than rats. OEHHA chose the dog study, which used the more sensitive species, as the critical study in deriving the PHG.

THIOBENCARB

Comment 1: "Overall the toxicological evaluation of Thiobencarb was appropriately performed and the relevant research was identified and discussed. The proposed PHG is founded in the body weight changes seen in a long term rat study. This appears to be the most sensitive endpoint."

Response 1: OEHHA acknowledges the comment.

Comments from Jennifer Seed (Independent Risk Assessment Consultant)

CARBOFURAN

Comment 1: "A number of studies have examined various endpoints of reproductive toxicity. However, there is little overlap in the species, duration of exposure, route of exposure, or administered doses, which makes a weight of evidence determination, and appropriate dose response relationships somewhat problematic. … The Pant et al (1995) study is the only study that provides strong evidence of male reproductive toxicity at low doses with good dose-response data. There are no studies that support the findings at similar doses, and in fact, most of the studies that do support the findings are at doses far exceeding those eliciting toxicity due to ChE inhibition. … [T]he US Environmental Protection Agency (US EPA) recommended that a new multigeneration reproductive toxicity study be conducted with special protocols to examine the effects observed by Pant et al (1995). Apparently, a new study has been submitted, and it did not replicate the findings of Pant et al (1995). This reviewer has not seen the study. It would be beneficial to OEHHA to review this study and see whether it impacts the selection of male reproductive toxicity as the critical endpoint for the derivation of the PHG. The study is designated as MRID 46688911 and is cited on page 17 of the US EPA document (EPA-HQ-OPP-2005-0162-0076)."

Response 1: OEHHA agrees that this new study (MRID 46688911) may add value to the discussion on the reproductive toxicity of carbofuran. However, OEHHA is not able to obtain this study. Without knowing details of the study, such as the doses tested, OEHHA cannot evaluate this study.

Additionally, OEHHA finds there is sufficient evidence of reproductive toxicity in the available database. Thus there is no reason for replacing male reproductive toxicity as the critical endpoint. While Pant et al. (1995) reported male reproductive effects at lower doses than the registrant-submitted reproductive studies, it is not the only study that showed reproductive/developmental effects at low doses.

Pant et al. (1997) found sperm abnormalities and degenerative testicular changes in male Druckery rat pups following in utero and lactational exposure to 0.4 mg/kg-day carbofuran. Jayatunga et al., (1998, as cited in DPR, 2006) observed statistically significant developmental effects in Wistar rats(including but not limited to decreases cranial length, fetal survival ratio, and time taken for fur to appear) at 0.4 mg/kg-day. Elayan et al. (2013) described a dose-dependent decrease in serum testosterone in male mice treated with 0.1 to 0.4 mg/kg-day carbofuran for 30 days. Another new study has been identified and added to the PHG document. Kobeasy et al. (2015) found significant effects on male reproductive toxicity, including decreased fertility index, sperm abnormalities, and effects on male sex organ weights and serum testosterone in albino rats treated with 2.4 mg/kg-day for 70 days. While the dose used was 10-fold higher than the LOAEL from Pant et al. (1995), the effects were more severe, including marked effects on testis weight and an almost 50% decrease in fertility index.

Comment 2: "It may also be beneficial to revisit the use of ChE [cholinesterase] inhibition as the "critical" endpoint. There are also some issues with using ChE inhibition for the derivation of the PHG, and many of those have been highlighted in this draft document. However, the issues have been well vetted in the scientific community (http://archive.epa.gov/scipoly/sap/meetings/web/pdf/carbofuransapfinal.pdf), and there is some precedence for using this endpoint for carbofuran."

Response 2: OEHHA is aware that ChE inhibition is often used as a toxicity endpoint for carbamates and organophosphates when appropriate. In the reference cited by this reviewer, the $BMDL_{10}$ of 0.031 mg/kg-day for ChE inhibition recommended by the scientific advisory panel was based on a single gavage exposure. Because PHGs are derived for chronic (lifetime) exposure scenarios, use of data from an acute single exposure study would not be appropriate. Based on OEHHA's review of the available toxicity data, male reproductive toxicity was identified as the critical health endpoint.

DIQUAT

Comment 1: "The US EPA recently posted a draft human health risk assessment for registration review of diquat (EPA-HQ-OPP-2009-0846-0022; http://www.regulations.gov/#!docketDetail;D=EPA-HQOPP-2009-0846;dct=FR+PR+N+O+SR). On pages 9-10 of that assessment, it is stated that a new immunotoxicity study was submitted and reviewed. This reviewer has not seen the study. OEHHA may wish to review it. However, the US EPA used the ocular toxicity (albeit they used the dog study) as the critical endpoint following oral exposure so it is unlikely that the immunotoxicity study would alter the choice of endpoint or dose-response assessment for the PHG."

Response 1: OEHHA has not evaluated this study as it is not readily available but it is unlikely to alter the choice of critical study or endpoint. US EPA did not provide a full summary but lists in Table A.2.2. of the 2015 draft human health risk assessment for diquat that the immunotoxicity NOAEL was 81 mg/kg-day, the highest dose tested, and the systemic NOEL was 23 mg/kg-day. These values are far higher than the $BMDL_{05}$ of 0.45 mg/kg-day, based on cataracts in rats, used to derive the PHG.

ENDRIN

Comment 1: "The best fitting model was the LogProbit model which yielded a $BMDL_{05}$ of 0.022 mg/kg-day. This value is a bit puzzling as it is below the NOAEL of 0.035 mg/kg-day in which there were 0/6 dogs exhibiting convulsions. It may be beneficial to provide some explanation for this result, and whether it should be used."

Response 1: OEHHA uses benchmark dose (BMD) modeling for point of departure (POD) determination, when the data are amenable to modeling, for the reasons outlined

in the Methodology section of the PHG document. In the case of the Jolley et al. (1969) study, the BMD_{05} (the dose that corresponds to a 5% increase in response over the controls) is 0.051 mg/kg-day. This represents a maximum likelihood estimate and is slightly higher than the experimental NOAEL of 0.035 mg/kg-day. In order to account for variability and uncertainty in the dataset, the 95% lower confidence limit of the BMD_{05} (the $BMDL_{05}$) is used to represent the POD. Because there were only 6 or 7 dogs in each dose group in the Jolley et al. (1969) study, the statistical power of the dataset is relatively low, resulting in large confidence limits and a lower $BMDL_{05}$. Using several selection critieria described in the PHG document, OEHHA chose the LogProbit model to describe the data and it yielded a $BMDL_{05}$ of 0.022 mg/kg-day. This estimate turns out to be slightly lower than the NOAEL of 0.035 mg/kg-day.

Comment 2: "The ADD is then calculated using a total uncertainty factor of 1000. This includes 10 for interspecies extrapolation and 100 for intraspecies variability. The rationale given for increasing the uncertainty factor for intraspecies variability is that endrin causes neurotoxic effects, and children are generally considered to be more sensitive to neurotoxicants. … If the uncertainty factor of 100 for intraspecies variability is retained it should be clear that this is a science policy decision."

Response 2: The use of an intraspecies uncertainty factor (UF) of 100 to account for the increased susceptibility of children to neurotoxicants is consistent with OEHHA's peer-reviewed risk assessment guidelines. These guidelines indicate that a default value of 10 is used for the toxicokinetic component of the intraspecies UF to allow for diversity, including infants and children, with no human kinetic data. The default value for the toxicodynamic component of the intraspecies UF is 10 when there is suspected additional susceptibility of children, as in the case of neurotoxicity (OEHHA, 2008).

PICLORAM

Comment 1: "In summary, the assumptions, findings, and conclusions reflect current scientific practices, and the draft PHG is based upon sound scientific knowledge, methods, and practices."

Response 1: OEHHA acknowledges the comment.

Comment 2: "The draft updated PHG document provides a review of studies conducted since the PHG was last published in 1997. None of the studies impact the selection of endpoint or dose response assessment for derivation of the PHG. This reviewer is not aware of any missing studies."

Response 2: OEHHA acknowledges the comment.

Comment 3: "The draft updated PHG uses sound science in the selection of relative liver weight as the critical endpoint. The methods used to derive the proposed PHG are conservative and well accepted to ensure that PHGs are health protective."

Response 3: OEHHA acknowledges the comment.

THIOBENCARB

Comment 1: "In summary, the assumptions, findings, and conclusions reflect current scientific practices, and the draft PHG is based upon sound scientific knowledge, methods, and practices."

Response 1: OEHHA acknowledges the comment.

Comment 2: "The draft updated PHG uses sound science in the selection of the Ashby et al (1984) study for derivation of the POD. The methods used to derive the proposed PHG are conservative and well accepted to ensure that PHGs are health protective."

Response 2: OEHHA acknowledges the comment.

Comments from David Stone (Oregon State University)

CARBOFURAN

Comment 1: "In addition to OEHHA's review, four additional research articles were identified in this review that OEHHA may wish to consider. These include: 1) a recent article that investigated the effect of carbofuran on mammalian oocytes (Cinar et al. 2015); 2) an investigation of carbofuran induced oxidative stress on rat brain activity (Jaiswal et al 2014); 3) the effect of carbofuran on the thyroid gland of male rats (Hadie et al. 2012); and 4) the induction of genotoxic effects in rat intestinal cells (Gera et al. 2011)."

Response 1: The suggested articles were reviewed and added to the PHG document but ultimately they were not selected for PHG derivation.

Comment 2: "OEHHA proposes to use a relative source contribution (RSC) of 0.8 to calculate a new PHG. It is unclear if 0.8 is consistent with past evaluations of carbofuran when California had active product registrations, or if the proposed RSC represents a change since the last evaluation."

Response 2: The previous PHG in 2000 applied a RSC of 0.2 because it was in active use and it was assumed that exposures to residues on food and in air would be greater than those from drinking water. However, because registration of carbofuran has since

been canceled in California and it is no longer in use, the main potential source of exposure to carbofuran is now drinking water. Thus, the default RSC of 0.8 is applied.

Comment 3: "OEHHA notes that carbofuran has not been detected in drinking water over the past three years (Table 2). While this is encouraging, additional databases, including federal water monitoring programs such as the U.S. Geological Survey, as well as other State databases, could also be evaluated to determine if carbofuran is present in ambient water sources that may be utilized for drinking water."

Response 3: PHGs are the health basis for California's drinking water regulatory standards (Maximum Contaminant Levels or MCLs). Monitoring data for public water supplies are the most relevant for providing some context in terms of potential exposures to regulated contaminants in tap water. As such, OEHHA presents recent monitoring data for public water supplies, which include drinking water sources (both ground and surface water) for systems that serve 15 or more connections or more than 25 people per day. Monitoring data are not used to calculate the PHG.

ENDRIN

Comment 1: "Few studies have examined adverse outcomes from endrin exposure. However, two potential studies were identified that were not included in the OEHHA's literature review. These include a retrospective study on neck cancer and organochlorines (Govett et al., 2011) and case reports of acute toxicity following intentional exposure (Moses and Peter, 2010)."

Response 1: These studies have been added to the PHG document**.**

RESPONSES TO MAJOR COMMENTS RECEIVED, FIRST COMMENT PERIOD (SEPTEMBER 2015)

Comments from the Sacramento River Source Water Protection Program

THIOBENCARB

Comment 1: "Page 4, Table 2 – The data sources for pesticides monitoring that are listed in this table do not include surface water data. This is a significant omission as many pesticides have been detected in surface waters that serve as existing or potential future sources of drinking water. California surface water pesticide monitoring data are available in two major databases—the California Department of Pesticide Regulation (DPR) surface water database (http://www.cdpr.ca.gov/docs/emon/surfwtr/surfcont.htm) and the California Environmental Data Exchange Network (CEDEN) database (http://www.ceden.org/index.shtml). California Water Board irrigated lands regulatory programs and the Central Valley Water Board Rice Pesticides Program also generate important and relevant data, but these data must be obtained from California Water Boards like the Central Valley Water Board, as they are not currently included in the DPR and CEDEN databases."

Response 1: PHGs are the health basis for California's drinking water regulatory standards (Maximum Contaminant Levels or MCLs). Monitoring data for public water supplies are the most relevant for providing some context in terms of potential exposures to regulated contaminants in tap water. As such, OEHHA presents recent monitoring data for public water supplies, which include drinking water sources (both ground and surface water) for systems that serve 15 or more connections or more than 25 people per day. DPR's Surface Water Database and the CEDEN database contain monitoring data for samples taken from rivers, creeks, agricultural drains, urban streams, and estuaries, which are not collected for the purpose of regulating public drinking water supplies. A PHG is calculated using data on a chemical's health effects. Monitoring data are not used to calculate the PHG.

Comment 2:
"Page 49, first sentence - Thiobencarb is only registered for use on rice (delete "in food crops such as")."

"Page 49, third sentence – Thiobencarb can be associated with an unpleasant bitter taste at sufficient concentrations. The specific threshold depends on individual taste sensitivity, which differs among the human population. Rice growers, the Central Valley Water Board, DPR and the Sacramento River Source Water Protection Program continue active coordination to minimize the risk of concentrations that exceed taste thresholds. We suggest that OEHHA correct this sentence to read: "Thiobencarb ~~was previously~~ can be associated with a taste problem (i.e., organoleptic property) in the drinking water primarily….""

Response 2: Editorial changes have been made accordingly.

Comment 3: "Page 49, fourth sentence – This sentence is incorrect and does not accurately reflect the information in the cited source. ... We suggest that OEHHA correct this sentence to read: 'Recently, methods of application have changed to reduce the incidental contamination outside of the rice fields~~; therefore, it is no longer detected along the Sacramento River~~ (DWWSP, 2011).'"

Response 3: OEHHA revised the sentence as recommended.

Comment 4: "Based on the enclosed data, we suggest OEHHA add a sentence such as 'In the last five years, thiobencarb has been detected multiple times in the Sacramento River watershed upstream of drinking water intakes, and has occasionally been detected in the Sacramento River near existing intakes.'"

Response 4: The enclosed data to which this comment refers are from the Rice Pesticide Program, managed by the Central Valley Water Board. As stated in the response to this reviewer's first comment, monitoring data for public water supplies (provided formerly by the California Department of Public Health and now by the State Water Resources Control Board) are the most relevant for providing some context in terms of potential exposures to regulated contaminants in tap water. Thus, OEHHA is only presenting monitoring data for public water supply wells. The suggested sentence is not added to the document.

Comment 5: "Page 53, last paragraph, first sentence – This sentence is inaccurate. Per information above and attached monitoring data (note detection limits today are as low as 0.1 µg/L), we suggest OEHHA correct this sentence to read: "Thiobencarb ~~is~~ has not recently been found at levels above its ~~detection limit~~ secondary MCL of 1 ppb in California public water systems ~~and wide-spread public exposure is not anticipated~~."

Response 5: The State Water Resources Control Board (SWRCB) is responsible for monitoring regulated contaminants in California's public water supplies. According to SWRCB's website, thiobencarb's detection limit for purposes of reporting (DLR) is 1 µg/L (accessed at: http://www.swrcb.ca.gov/drinking_water/certlic/drinkingwater/Documents/EDTlibrary/storlist.xls; last updated January 27, 2016). However, the suggested sentence correction is consistent with the point being made. OEHHA revised the sentence as recommended.

REFERENCES

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