Office of Environmental Health Hazard Assessment

Joan E. Denton, Ph.D., Director
Headquarters • 1001 I Street • Sacramento, California 95814
Mailing Address: P.O. Box 4010 • Sacramento, California 95812-4010
Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612

Linda S. Adams
Secretary for Environmental Protection

Arnold Schwarzenegger
Governor

M E M O R A N D U M

TO: Allan Hirsch
Chief Deputy Director

VIA: George V. Alexeeff, Ph.D., D.A.B.T.
Deputy Director for Scientific Affairs

VIA: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Branch

Robert A. Howd, Ph.D., Chief
Water Toxicology Section
Pesticide and Environmental Toxicology Branch

Charles B. Salocks, Ph.D., D.A.B.T, Chief
Pesticide Epidemiology Section
Pesticide and Environmental Toxicology Branch

FROM: Catherine Caraway, Associate Industrial Hygienist
Pesticide Epidemiology Section
Pesticide and Environmental Toxicology Branch

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SUBJECT: UPDATE OF THE DINOSEB PUBLIC HEALTH GOAL

Under the Calderon-Sher California Safe Drinking Water Act of 1996, the Office of Environmental Health Hazard Assessment (OEHHA) develops public health goals (PHGs) for regulated chemicals in drinking water and reviews and updates the risk assessments every five years (Health and Safety Code Section 116365(e)(1)) or when possible. This memorandum represents an update of the literature review and evaluation for the existing PHG of 14 parts per billion (ppb) for dinoseb (OEHHA, 1997). Our re-evaluation supports the previous PHG derivation in 1997, and no new data would justify a significant change to the document.

Summary of Review

OEHHA has reassessed the available toxicity data on dinoseb (2-sec-butyl-4,6-dinitrophenol) to determine whether significant new data are available since the current public health goal (PHG) was developed for this pesticide in 1997. OEHHA also determined whether changes in risk assessment methods since the publication of the PHG would justify a change in the health-protective value. Use of this dinitrophenolic compound was canceled in the late 1980s due to concerns about birth defects and reproductive hazards. Because the half-life of dinoseb in environmental media is fairly short (14 to 100 days in various media; U.S. EPA, 2009), continued human exposure to this substance in drinking water is expected to be none or minimal.

Only one significant new toxicity study was found in an updated literature search. In a screening test for reproductive/developmental toxicity, Matsumoto *et al*. (2008) gave daily gavage doses of 0, 0.78, 2.33, or 7.0 mg/kg-day dinoseb suspended in corn oil to Sprague-Dawley rats. Six male rats per group were treated with dinoseb for 42 days beginning 14 days before mating. Twelve females per group were treated for 44 to 48 days from 14 days before mating to day six of lactation, when they and the pups were sacrificed and examined. In addition, recovery groups of six males and six non-pregnant females at each dose were treated for 42 days and sacrificed 14 days post-treatment. Behavioral observations were made once per week for one hour following treatment and a more extensive sensory-motor test was conducted on six male rats following treatment on day 40 and six females on lactation day 4. Standard blood and clinical chemistry parameters were measured; urinalysis was conducted on 24-hr urines collected during the administration period (time point not stated). Adults and pups were given an extensive necropsy evaluation.

No deaths were observed in any adult male group or in the female recovery groups. However, in the pregnant females, 8 out of 12 at the highest dose died and two were moribund during late pregnancy. A significant decrease in body weight gain at this dose was observed in both sexes, and food consumption was slightly increased (as expected for an uncoupler of oxidative phosphorylation, as in dinitrophenolic compounds). There was also increased food consumption after treatment ceased in the male high dose recovery group. The ‘main’ group males had significant dose-related increases in hematocrit, although this was associated with a decreased control value (see Table 1 and explanation below). No hematocrit changes were observed in the recovery group nor in the female rats. The red blood cell (RBC) count was elevated only at the lowest dose in both males and females, but decreased at the highest dose in the recovery males. Hemoglobin and prothrombin time (PT) were significantly increased at the two highest doses in males.

Table 1. Effects of Dinoseb on Selected Blood Parameters in Male Rats

Parameter	**Dose (mg/kg-day)**			
	0	**0.78**	**2.33**	**7.0**
Main groups				
RBCs (10^4/µL)	801 ± 13[a]	844 ± 30*	833 ± 31	834 ± 29
Hemoglobin (g/dL)	14.9 ± 0.5	15.5 ± 0.7	15.7 ± 0.5*	16.2 ± 0.5**
Hematocrit (%)	43.9 ± 0.8	46.4 ± 1.9*	46.6 ± 1.4**	47.7 ± 1.2**
Recovery groups				
RBCs (10^4/µL)	858 ± 21	831 ± 22	852 ± 38	817 ± 22*
Hemoglobin (g/dL)	15.9 ± 0.4	15.3 ± 0.4	15.6 ± 1.1	15.8 ± 0.3
Hematocrit (%)	46.8 ± 0.9	45.2 ± 1.2	46.6 ± 3.4	46.0 ± 1.0

[a] Values are given as the mean ± standard deviation
* Significantly different from the control group ($p<0.05$)
** Significantly different from the control group ($p<0.01$)

Males at the highest dose had an increase in relative brain weight and also showed a decrease in sperm motility and an increase in the rates of abnormal sperm, abnormal tail, and abnormal head. Similar sperm effects were found in the high-dose recovery group. Females exhibited no apparent treatment-related effects on any organ weights or organ histopathology except a decrease in abnormal extramedullary hematopoiesis in the spleen in the 2.33 mg/kg-day group. The number of dams delivering live pups was significantly decreased at the highest dose, due to the high death rate of the dams. No treatment-related effects were observed on the standard reproductive parameters (number of births, stillbirths, sex ratio, pup body weight, etc.) at the 0.78 and 2.33 mg/kg-day doses.

The authors noted no treatment-related effects on the clinical observations and behavioral tests in any of the treated and recovery groups, for both males and females. This may indicate that the effects leading to the death of most of the high-dose females were not apparent at the times the observations and tests were carried out. Clinical chemistry analyses of blood and urine also revealed no significant differences among groups except for increased blood creatinine at 7.0 mg/kg-day in males.

The authors interpreted the treatment-related increase in hematocrit in males as an indicator of polycythemia, resulting from a homeostatic response to low oxygen levels in cells caused by uncoupling of oxidative phosphorylation. However, the lower hematocrit in the main control group makes this of questionable biological significance. Upon our request, the study authors provided historical control data, revealing that the main control group hematocrit values are on the low side of the historical range (46.1 +/- 2.4, with a two-standard deviation range of 41.3 to 50.9). The hematocrit values for all treated male groups are also well within the historical range and not significantly different from the recovery group values. Nevertheless, the study authors identified the hematocrit changes as indicative of adverse effects, and the lowest dose of 0.78 mg/kg-day as the lowest observed adverse effect level (LOAEL) for the study. The authors also noted that the prothrombin changes were within historical values, and did not consider them to be biologically relevant.

The original PHG written in 1997 is based on a LOAEL of 1 mg/kg-day for reproductive effects identified in adult mice (Brown, 1981). The endpoints were cystic endometrial hyperplasia in female mice and hypospermatogenesis and atrophy/degeneration of the testes in male mice at the LOAEL of 1 mg/kg-day. A second reproduction study on rats by Irvine and Armitage (1981) evaluated the effects of dinoseb over three generations and demonstrated decreased fetal weights and a decrease in pup body weights at all doses (1, 3 and 10 mg/kg-day). The presumed LOAEL (0.78 mg/kg-day) in this study of Matsumoto *et al*. (2008) is similar to the LOAELs (1 mg/kg-day) of the two other studies; the questionable biological significance of the effect would not in itself justify a revision of the PHG value.

Since dinoseb was last reviewed, we have updated our methods to better quantify exposures in representative populations and now routinely use drinking water consumption values intended to provide more protection for sensitive and highly-exposed populations. In this regard, the PHG could be recalculated to include exposure values for pregnant females, based on the endometrial hyperplasia in female mice in Brown (1981) and the decreased weights of rat fetuses and pups in Irvine and Armitage (1981). On the other hand, no effects were observed in pregnant female rats or their offspring at 0.78 and 2.33 mg/kg-day in the more recent study of Matsumoto *et al*. (2008), and the hypoxic effects of dinitrophenolic compounds are relatively well understood. It should also be noted that dinoseb levels have not exceeded the Maximum Contaminant Level (MCL) of 7 ppb for at least the last decade. Dinoseb was reportedly found in California drinking water at 2 ppb (the detection limit) in 1999 (EWG, 2009). Thus, significant public exposure is not anticipated to occur, as would be expected for this long-canceled pesticide.

Conclusion

The available new data do not indicate a need for revising the PHG level or the PHG document for dinoseb. Because the California MCL of 7 ppb is lower than the current PHG level of 14 ppb, we also see no need to revise the document based on the recommended changes in risk assessment methods (use of benchmark dose modeling or higher drinking water consumption values) since publication of the original review.

References

Brown D (1981). Dinoseb: A 100 week oral (dietary) toxicity and carcinogenicity study in the mouse. Hazelton Laboratories Europe, Ltd. Prepared for Dow Chemical Pacific, Ltd., Hong Kong. EPA MRID 00152762.

EWG (2009). Environmental Working Group – National Tapwater Quality Database. The State of California – Dinoseb Summary for California. Accessed July, 2009 at http://www.ewg.org/tapwater/yourwater/system_contam_testing.php?pwsid=CA3610120&contam=2041.

Irvine L, Armitage A (1981). 2-secbutyl-4,6-dinitrophenol (Dinoseb): Three generation reproductive performance study in the rat (dietary). Hazelton Laboratories Europe, Ltd. Prepared for Agricultural Chemical, Dow Chemicals Pacific, Ltd., Hong Kong. U.S. EPA Accession No. 259399

Matsumoto M, Furuhashi T, Poncipe C, Ema M (2008). Combined repeated dose and reproductive/developmental toxicity screening test of the nitrophenolic herbicide dinoseb, 2-sec-butyl-4,6-dinitrophenol, in rats. Environ Toxicol 23(2):169-83.

U.S. EPA (2009). Drinking Water Contaminants. Technical Factsheet on: Dinoseb. U.S. Environmental Protection Agency, Washington, DC. Accessed at: http://www.epa.gov/safewater/hfacts.html.