REVISED FINAL STATEMENT OF REASONS
22 CALIFORNIA CODE OF REGULATIONS

SECTION 12805. SPECIFIC REGULATORY LEVELS: REPRODUCTIVE TOXICANTS

This is the Final Statement of Reasons for specific regulatory levels for one chemical, sodium dimethyldithiocarbamate**,** listed as known to the State to cause reproductive toxicity under the Safe Drinking Water and Toxic Enforcement Act of 1986 (hereinafter "the Act" or Proposition 65; Health and Safety Code section 25249.5 *et seq*.). On July 2, 2004, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to adopt regulatory levels for ten chemicals listed pursuant to the Act as known to the State to cause cancer or reproductive toxicity (Title 22, California Code of Regulations §12000). The Notice set forth proposed regulatory levels for two chemicals listed as known to cause cancer (1,2-dichloropropane and naphthalene) for adoption in Title 22, Cal. Code of Regs. §12705(b) and, for eight chemicals listed as known to cause reproductive toxicity (1,2-dibromo-3-chloropropane, disodium cyanodithioimidocarbonate, ethyl dipropylthiocarbamate, ethylene glycol monomethyl ether, ethylene glycol monomethyl ether acetate, methyl bromide as a structural fumigant, sodium dimethyldithiocarbamate and thiophanate-methyl) for adoption in §12805. The Initial Statement of Reasons set forth the grounds for the proposed regulations. Pursuant to the Notice of Proposed Rulemaking, a public comment period was held between July 2 and August 23, 2004, and a public hearing was held on August 23, 2004.

On July 2, 2004, OEHHA provided the technical support documents forming the basis for the proposed regulatory levels for chemicals listed as known to the State to cause reproductive toxicity to the members of the Developmental and Reproductive Toxicant (DART) Identification Committee for their review and comment as allowed by Title 22, Cal. Code of Regs., §12302(e). No comments were received from any committee members.

This regulation hereby adopts regulatory levels for sodium dimethyldithiocarbamate, one chemical included in the Notice of Proposed Rulemaking. Regulatory levels for eight other chemicals included in the Notice of Proposed Rulemaking were adopted and effective on January 22, 2005 (1,2-dichloropropane, 1,2-dibromo-3-chloropropane, disodium cyanodithioimidocarbonate, ethyl dipropylthiocarbamate, ethylene glycol monomethyl ether, ethylene glycol monomethyl ether acetate, methyl bromide as a structural fumigant and thiophanate-methyl). A regulation on the remaining chemical (naphthalene) included in the Notice of Proposed Rulemaking will be adopted at a later time.

UPDATE OF INITIAL STATEMENT OF REASONS

All data, studies, reports, or other documents relied on for this regulation were identified in the Initial Statement of Reasons of July 2, 2004, except as noted immediately below.

The OEHHA document referenced in the Initial Statement of Reasons as "OEHHA (2004i)" entitled "Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Sodium Dimethyldithiocarbamate for Oral Exposures" laid out the reasoning for the MADL for Sodium Dimethyldithiocarbamate (SDDC), and continues to serve as the basis for the MADL. In order to illustrate the responses to several of the comments received on this document and presented below, a revision of this OEHHA technical support document is included with this Final Statement of Reasons (OEHHA 2005) as Attachment 1. All changes are noted in underline/strikeout in Attachment 1. These revisions do not alter the MADLs for SDDC, and this revised technical support document is for informational purposes only and is not substantially altered from the original document.

The revisions are described below.

A sentence describing studies of zinc dimethyldithiocarbamate (ziram) has been deleted (page 2; final sentence of the third paragraph under "Study Selection") and a sentence describing studies of potassium dimethyldithiocarbamate (PDDC) has been revised (page 3; first complete sentence on the page). These changes more accurately reflect the consideration given to information on related dimethyldiothiocarbamate salts in developing the MADL. Two references pertaining to ziram (Giavini et al. 1983), and PDDC (Rodwell 1988b), were deleted.

Wording has been added in OEHHA (2005) to specify that the NOEL is based on the skeletal variant endpoint, which OEHHA finds to be related to sodium dimethyldithiocarbamate exposure, and not the resorption endpoint, which may not be treatment related (page 3; third sentence on the page).

In addition to revisions to OEHHA (2005), three documents were referenced in the responses to comments below that were not identified in the OEHHA (2004i) document and were not included in the Initial Statement of Reasons of July 2, 2004. They are as follows:

Harris SB and DeSesso JM. Practical guidance for evaluating and interpreting developmental toxicity tests. J Hazard Materials 39:245-266, 1994.

Szabo KT. Congenital Malformations in Laboratory and Farm Animals. Academic Press, San Diego, 1989.

U.S. Environmental Protection Agency Guidelines for Reproductive Toxicity Risk Assessment. Federal Register 61:(212) 56274-56322, 1996.

SUMMARY AND RESPONSE TO COMMENTS RECEIVED

Comments on the proposed rulemaking for sodium dimethyldithiocarbamate (SDDC) were received from ALCO Chemical. Sections of the ALCO comments directly relevant to the proposed rulemaking concern identification of Lowest Observed Effect Levels

(LOELs) and No Observed Effect Levels (NOELs) from the rat and rabbit teratology studies (p. 3 and p. 5 of the ALCO comments). They are addressed in detail below. Other comments are related to the original listing of SDDC, and are not relevant to the present rulemaking. These comments are noted below but are not responded to since they do not pertain to the present rulemaking.

Comment:
ALCO reviews the basis for the original listing of SDDC, concludes that the rationale on which the State relied was flawed, and "respectfully urge[s] OEHHA to correct the record with regard to the unfounded listing of SDDC as a reproductive hazard."

Response:
OEHHA notes this comment. However, this and several related comments submitted by ALCO do not address the development of the MADL. These comments are not relevant to the Proposed Rulemaking and therefore OEHHA has not responded to them in this Final Statement of Reasons.

Comment:
ALCO objects to the discussion of PDDC (ALCO p. 4) and ziram (ALCO p. 6) studies in the OEHHA SDDC document.

Response:
While OEHHA does not agree with the ALCO assessment of the relevance of the ziram studies, their discussion is not essential to MADL development and has been removed from the OEHHA document. The discussion of the PDDC study has been retained because it was cited by the authoritative body (U.S. EPA) in the document used as the basis of listing (U.S. EPA, 1994, Final Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. Federal Register 59:(229) 61432, 1994), and was considered in the process of MADL development. However, a study of SDDC in the same strain of rabbit was determined to be the most sensitive study deemed to be of sufficient quality, since it identified a lowest observable effect level that was below the lowest observable effect level in the PDDC study. In addition the SDDC study identified a NOAEL, while the PDDC study did not.

Comment:
The finding of rabbit supernumerary ribs endpoint, the endpoint selected for MADL development, was not dose related (ALCO p.3, item 1). This is also brought forward in the ALCO critique of the SDDC rat study, and the same concern is raised for the incidence of distended renal pelvis/ureter (ALCO p. 5, item 1). ALCO notes that for both the SDDC and PDDC studies in rabbits, toxicologists in the California Environmental Protection Agency, Department of Pesticide Regulation concluded that there were no adverse effects (ALCO p. 3, item 3 and p. 4). ALCO states: "It is a generally accepted principle among experts in the field that the establishment of a dose-response is critical in determining the significance of extra ribs" (ALCO p. 4).

Response:

No citation or other reference is provided to support the statement that the establishment of dose response is critical in determining the significance of extra ribs. OEHHA notes that the two SDDC developmental toxicology studies were consistent in exhibiting elevated incidence of extra ribs in the mid dose but not the high dose group (Study 1 - Weir PJ. Teratogenicity Study in Rabbits of MRD-86-933 [Aquatreat SDM: Approximately 40% Sodium Dimethyldithiocarbamate]. Laboratory Project ID 293334RB, 1987. Study 2 - Exxon Biomedical Sciences, Inc., East Millstone, NJ and Weir PJ Teratogenicity Study in Rats of MRD-86-933 [Aquatreat SDM: Approximately 40% Sodium Dimethyldithiocarbamate]. Laboratory Project ID 293334, 1987. Exxon Biomedical Sciences, Inc., East Millstone, NJ). OEHHA recognizes that many factors can lead to dose response data where an effect occurs at a lower dose but not at a higher dose. In developmental toxicity studies, for example, it is recognized that the most highly affected fetuses at higher doses can die and be resorbed, and thus not contribute to the malformation/variation tallies (Harris SB and DeSesso JM. Practical guidance for evaluating and interpreting developmental toxicity tests. J Hazard Materials 39:245-266, 1994).

A point particularly relevant to the SDDC studies is effective dose as compared to intake. Although the applied dose of SDDC increased from the mid to the high dose level, the effective dose (i.e., the dose reaching target tissues) for this compound is highly dependent on pH, which determines compound stability. The formulated compound is extremely basic (pH=11-13) and is administered in water solution directly into the acidic gastric contents. At the highest doses, the pH of the gastric contents after dosing may be altered so as to reduce dissociation and absorption of SDDC**.**

In terms of biological significance of the observed effects, it is generally assumed in developmental toxicity risk assessment that "an agent that produces an adverse developmental effect in experimental animal studies will potentially pose a hazard to humans following sufficient exposure during development [and]….the types of developmental effects seen in animal studies are not necessarily the same as those that may be produced in humans." (U.S. Environmental Protection Agency (1991) Guidelines for Developmental Toxicity Risk Assessment. Federal Register 56:63798-826, 1991). In this case, extra ribs can reflect a homeotic shift, a failure of the genetic program for body patterning, which is broadly relevant to normal development in all species. The distended renal pelvis/ureter endpoint, is not used as the basis for MADL development, so no further response is provided.

OEHHA scientists with specific expertise in reproductive toxicity have conducted a review of the studies of SDDC and PDDC in rabbits as these relate to the establishment of an MADL for SDDC. Although OEHHA recognizes the expertise of staff in the Cal/EPA Department of Pesticide Regulation (DPR), reviews conducted for DPR's programmatic purposes are not necessarily directly comparable or applicable to those conducted for implementation of Proposition 65.

Comment:
Litter-based statistics were not used (ALCO p. 3, item 2).

Response:
With regard to litter-based statistics, the use of litter incidence (number of litters with at least one fetus affected) is valuable for rare fetal abnormalities. This prevents the presence of the defect in many fetuses of one or two litters from inappropriately influencing the group comparisons. However, supernumerary ribs, as the commenters point out, are not a rare abnormality. This allows the opportunity to use litter-based statistics to determine the incidence (affected/total) in each litter and to compare these incidences by parametric statistics. OEHHA used this approach to determine that there was a higher mean number of fetuses per litter with supernumerary ribs in the 100 mg/kg group than the control group and that this difference was statistically significant. Thus litter-based statistics also support a treatment effect at this dose.

Comment:
Supernumerary ribs are a common variation in rabbit teratology studies (ALCO p.3, item 2).

Response:
Further consideration of the data using a less common skeletal variation supports the identification of a treatment effect in the 10 mg/kg/d group. While a supernumerary rib, short or rudimentary, is a common occurrence in rabbit fetuses (33% in the control group of this study), two supernumerary ribs in a fetus is less common (8% of fetuses in the control group). In addition to a higher incidence of fetuses having at least one supernumerary rib, OEHHA found that the 10 mg/kg group also had a higher incidence than controls of fetuses with two supernumerary ribs that was statistically significant.

Comment:
Variation in incidence of supernumerary ribs occurs with season and colony (ALCO p.3, item 2)

Response:
In accord with current standards of study design, the study has a concurrent control group. Thus the study design explicitly addresses the issue of colonies and seasonal variations. Although supernumerary ribs are a common variation in rabbit fetuses, the incidence has been shown to be increased by a variety of maternal treatments (Szabo KT. Congenital Malformations in Laboratory and Farm Animals. Academic Press, San Diego, 1989).

OEHHA notes that the detection of a treatment effect for the relatively common variation supernumerary ribs is to an extent dependent on the data analysis strategy of the study report. The investigators tested only two variations statistically because the expected incidence of all other variations was too small for the χ-square test used.

Comment: ALCO states that the decreased number of resorptions at the mid dose in the rabbit study should not be called a fetal effect (ALCO bottom p. 4).

Response:
OEHHA agrees that this is not necessarily an adverse effect of treatment with SDDC and may be associated with a lower ovulation rate in the mid-dose group. Wording has been added to the MADL document (OEHHA 2005) to specify that the NOEL is based on the skeletal variant endpoint and not the resorption endpoint.

Comment:
The EPCRA listing of SDDC was based on a study with PDDC (p.7, bullet 1)

Response:
ALCO correctly states that the U.S. EPA identification of SDDC as causing developmental toxicity in the EPCRA regulatory notice was not based on an SDDC study, but rather on a PDDC study. However, while OEHHA is limited in listing the chemical to consideration only of studies in the administrative record of the authoritative body, this restriction does not apply to establishing a MADL. Rather, the regulatory requirement is that "the assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing the chemical" (Title 22, California Code of Regulations, section 12803(a)). OEHHA considers the relevant studies of SDDC to be of comparable scientific validity to the study of PDDC which formed the basis for listing SDDC. Thus, OEHHA has used the most sensitive study of SDDC deemed to be of sufficient quality (Title 22, California Code of Regulations, section 12803(a)(4)) in establishing the MADL.

Comment:
The comments conclude with a summary of major points that the commenters believe have not been appropriately addressed by the State. These are presented as seven bullet items. Each bullet item is reproduced below, followed by OEHHA's response.

- The initial listing of SDDC as a potential developmental toxicant under EPCRA, and its subsequent adoption for listing by the State under Proposition 65, were based on an interpretation of results of a single study with potassium dimethyldithiocarbamate, <u>not</u> SDDC.

  Response: This comment does not address the development of the MADL, which is the subject of the current rulemaking; therefore, no response is necessary.

- Evidence is lacking to support the theory implied by the EPCRA listing that a concordance of indicators of toxicological potential exists among the dithiocarbamate salts as a class. Consequently, an interpretation of potential developmental toxicity attributable to the potassium salt should not have been used as the basis for listing the sodium salt by analogy while ignoring direct evidence of no adverse effect with SDDC.

  Response: This comment does not address the development of the MADL, which is the subject of the current rulemaking; therefore, no response is necessary.

- In a definitive oral teratology study in rabbits, Wier (*1987a*) determined that SDDC was not a developmental toxicant in this species. Expert toxicologists in the California EPA formally reviewed the study data and confirmed that the study was sufficient to demonstrate that there was no adverse developmental effect in rabbits up to and including the highest dose tested (100 mg/kg/day of formulated product, equivalent to 40 mg/kg/day SDDC).

  Response: OEHHA notes that both this SDDC developmental toxicology study (Study 1 - Weir PJ. Teratogenicity Study in Rabbits of MRD-86-933 [Aquatreat SDM: Approximately 40% Sodium Dimethyldithiocarbamate]. Laboratory Project ID 293334RB, 1987) and another SDDC developmental toxicology study (Study 2 - Exxon Biomedical Sciences, Inc., East Millstone, NJ and Weir PJ Teratogenicity Study in Rats of MRD-86-933 [Aquatreat SDM: Approximately 40% Sodium Dimethyldithiocarbamate]. Laboratory Project ID 293334, 1987. Exxon Biomedical Sciences, Inc., East Millstone, NJ) were consistent in exhibiting elevated incidence of extra ribs in the mid dose but not the high dose group. As discussed above, OEHHA recognizes that many factors can lead to dose response data where an effect occurs at a lower dose but not at a higher dose. In developmental toxicity studies, for example, it is recognized that the most highly affected fetuses at higher doses can die and be resorbed, and thus not contribute to the malformation/variation tallies. Although OEHHA recognizes the expertise of staff in the Cal/EPA Department of Pesticide Regulation (DPR), reviews conducted for DPR's programmatic purposes are not necessarily directly comparable or applicable to those conducted for implementation of Proposition 65. No change was made based upon this comment.

- In a definitive oral teratology study in rabbits with potassium dimethyldithiocarbamate (PDDC), the NOEL for maternal and developmental effects was found at the lowest dose tested. Significant maternal toxicity (including mortality) occurred in the mid and high dose groups. California EPA toxicologists concluded that no meaningful data were available for evaluation of developmental effects at the highest dose, and there was "no preponderance of any specific finding" in the mid dose group, in which a general increased incidence of skeletal differences was attributable to maternal toxicity

  Response: The simple co-occurrence of maternal and developmental toxicity does not establish that the developmental effects are secondary to maternal toxicity, nor was that stated in the Cal/EPA Department of Pesticide Regulation (DPR) review of the study. DPR stated that "possible adverse effects (early resorptions, total litter loss, increase in skeletal malformations/variations at 75 mg/kg with no preponderance of any specific finding)" in the mid dose group, in which a general increased incidence of skeletal differences was attributable to maternal toxicity. For the effects other than skeletal differences, DPR stated that they *may* be related to the maternal effects. Although OEHHA recognizes the expertise of staff in DPR, reviews conducted for DPR's programmatic purposes

are not necessarily directly comparable or applicable to those conducted for implementation of Proposition 65.

- There is no concordance of developmental findings between SDDC and PDDC in rabbits that can be cited to justify using the PDDC data to support OEHHA's hypothesis of a non-dose-related effect with SDDC. Further, the initial rational for listing under EPCRA (US EPA, 1994b), which was based strictly on interpretation of results of a rabbit study with PDDC, has been shown to be invalid. The theory advanced for listing under EPCRA was: "*By analogy to potassium dimethyldithiocarbamate, sodium dimethyldithiocarbamate can reasonably be anticipated to cause fetotoxicity, postimplantation loss and malformations.*" The data from the study in rabbits with SDDC clearly show that the prediction made by the U.S. EPA was incorrect. OEHHA has acknowledged that postimplantation loss was actually significantly reduced in rabbits treated with SDDC (mid dose group). As noted above, other expert toxicologists within the California EPA have confirmed that SDDC exhibits no adverse developmental or reproductive effects in rabbits or rats.

  Response: This comment does not address the development of the MADL, which is the subject of the current rulemaking; therefore, no response is necessary.

- Substantial evidence has been presented in the review and discussion above that is counter to OEHHA's assertion that distended renal pelvis/ureter were related to treatment in rats with SDDC. There was no dose relationship, and incidences appeared to be random; *e.g.*, fetal incidences of this observation were highest in the low dose group, and litter incidences were highest in the mid dose group, but the high dose group was comparable to the control group with respect to both fetal and litter incidences. OEHHA indicated that *"(t)he developmental toxicity LOEL for this study was 1.6 mg/kg-day based on this effect; no NOEL was available since 1.6 mg sodium dimethyldithiocarbamate/kg-day was the lowest dose used."* In contrast, other California EPA toxicologists (DPR Medical Toxicology Branch) found "*no adverse effect*" and established the "*Nominal developmental NOEL ≥500 mg of Aquatreat/kg.*" (the highest dose level tested in this study; equivalent to 200 mg/kg/day).

  Response: Distended renal pelvis/ureter is not used as the basis for MADL development, so no further response to this comment is necessary.

- OEHHA suggested that a published report (*Giavini et al., 1983*) of renal pelvic dilatation in fetuses of rats given high oral doses of ziram (zinc dimethyldithiocarbamate) may be supportive of a finding of developmental toxicity with SDDC by analogy. ALCO believes that this theory is flawed for several reasons, as discussed in greater detail above. It is inappropriate to compare SDDC with heavy metal salts such as ziram. Further, the Giavini teratology study does not meet current regulatory standards and did not use an adequate number of pregnant females/group. In addition, renal pelvic dilatation

was increased only in the high dose group, at which more than half of the mated females died. Additional studies presenting more robust data, but with negative results, were not included in the OEHHA justification for the proposed MADL. Notably, other toxicologists within California EPA have reviewed the more extensive database of reproductive studies in rats and teratology studies in rats and rabbits, and they have determined that ziram did not cause adverse reproductive or developmental effects.

Response: While OEHHA does not agree with the ALCO assessment of the relevance of the ziram studies, consideration of them was not essential to MADL development. Discussion of these studies has been removed from the revised OEHHA technical support document (OEHHA 2005) to avoid confusion on this point.

In conclusion, the ALCO comments raise issues that were carefully considered by OEHHA but were not found to alter the SDDC MADL value. Clarifying changes have been made to the document supporting MADL development in response to the comments.

SUMMARY AND RESPONSE TO COMMENTS RECEIVED DURING THE NOTICE PERIOD OF JUNE 21 THROUGH JULY 6, 2005

No comments were received regarding the revised technical support document for SDDC.

SUMMARY AND RESPONSE TO COMMENTS RECEIVED DURING THE NOTICE PERIOD OF JULY 1, 2005 THROUGH JULY 18, 2005

No comments were received regarding the addition to the rulemaking file of documents and information relied upon by OEHHA in adopting the proposed regulatory level for SDDC.

ALTERNATIVES DETERMINATION

In accordance with Government Code Section 11346.5(a)(7), OEHHA has, throughout the adoption process of this regulation, considered available alternatives to determine whether any alternative would be more effective in carrying out the purpose for which the regulations were proposed, or would be as effective and less burdensome to affected private persons than the proposed action. OEHHA has determined that no alternative considered would be more effective, or as effective and less burdensome to affected persons, than the proposed regulation.

For chemicals listed under the Act as known to cause reproductive toxicity, the Act exempts discharges to sources of drinking water and exposures of people without provision of a warning if the exposure produces no observable effect on reproduction assuming exposure at 1,000 times the level in question, or the discharged amount is at or below this level (Id.). The Act does not specify numerical levels of exposure where there

would be no observable effect given an exposure 1,000 times the level in question, i.e., the maximum allowable dose level (MADL).

The purpose of this regulation is to provide "safe harbor" levels for certain chemical exposures. This regulation establishes MADLs for a chemical that causes reproductive toxicity. The discharge prohibition does not apply to exposures at or below these levels and warnings regarding reproductive toxicity concerns are not required for exposures at or below these levels. Thus, these levels will allow persons subject to the Act to determine whether a given discharge to sources of drinking water or exposure of people involving these chemicals is subject to the warning requirement and discharge prohibition provisions of the Act (Health and Safety Code sections 25249.6 and 25249.5 respectively).

Although Title 22, Cal. Code of Regs., §12803 describes principles and assumptions for conducting risk assessments to derive safe harbor levels, many businesses subject to the Act do not have the resources to perform these assessments. Yet each business with ten or more employees needs the ability to determine whether its activities or products are subject to the discharge prohibition or warning requirements of the Act. Given the wide use or occurrence of the chemicals covered by this regulation, the absence of this regulation would leave numerous businesses without an efficient way of determining if they are in compliance with the Act without the expenditure of significant resources on their part.

LOCAL MANDATE DETERMINATION

OEHHA has determined the regulatory action will not pose a mandate on local agencies or school districts nor does it require reimbursement by the State pursuant to Part 7 (commencing with Section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from the proposed regulatory action. It should be noted that Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, the proposed regulations do not impose any mandate on local agencies or school districts.