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MEMORANDUM

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DATE: August 31, 1998

SUBJECT: COMMENTS ON THE DEPARTMENT OF PESTICIDE REGULATION'S DRAFT RISK CHARACTERIZATION DOCUMENT FOR THE PESTICIDE ACTIVE INGREDIENT NALED

The purpose of this memorandum is to update our memorandum dated June 16, 1998, in which we provided general comments on the draft naled risk characterization document (RCD) prepared by the Department of Pesticide Regulation (DPR). Naled is a high priority active ingredient under the Birth Defect Prevention Act of 1984 (SB 950) and also is a candidate for evaluation under the Toxic Air Contaminant Identification and Control Act of 1983 (AB 1807). One active metabolite and degradation product of naled, dichlorvos (DDVP), is listed under the California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) as a chemical known to the State of California to cause cancer.

This memorandum provides more detailed explanation of our general concerns as well as additional specific comments on the draft naled RCD. This current, more detailed memorandum should replace the June 16, 1998, memorandum. As before, upon completion of our review of the draft RCD for naled we conclude that significant revisions of the draft are required.

In reviewing the draft RCD for naled, we considered the following information: 1) the draft naled RCD (May 7, 1998); 2) the draft human pesticide exposure assessment for naled prepared by the Worker Health and Safety Branch (December 19, 1997); 3) the summary of the

draft dichlorvos RCD (October 19, 1994); 4) U.S. Environmental Protection Agency (U.S. EPA) tolerances; 5) the calculations (dosage estimation for animals from an inhalation study, dosage estimation for animals in a dietary study, and margin of safety); 6) the available toxicology summaries from DPR; 7) the acute dietary analysis of acute exposure to naled and DDVP; 8) the chronic dietary analysis of chronic exposure to naled and DDVP; and 9) the results of our literature search.

Thank you for the opportunity to comment on the draft RCD for naled. The comments are provided as follows. If you have any questions about our comments, please contact me or Dr. Michael J. DiBartolomeis at (510) 540-3063.

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GENERAL COMMENTS

The draft risk characterization document for naled includes a summary and critique of the data available in DPR's registration data base. The appendices include somewhat more detailed information. We found the inclusion of summary tables helpful in accessing some of the more critical information.

Literature Search

It is not clear from reviewing the draft RCD whether there was a complete search of the open literature to identify relevant articles on the toxicology, mechanism of action, and pharmacokinetics of naled and its major breakdown products. Pertinent information published in the open literature, in addition to information submitted by the registrant, should be considered in preparing a risk assessment for any pesticide active ingredient. If a complete search was conducted, and no relevant data were identified, we recommend that this be made clear in the naled RCD before it is finalized.

We conducted a literature search for naled, dichlorvos and their major breakdown products using the current 1998 on-line and CD-ROM based resources including MedLine/ToxLine and the Registry of Toxic Effects of Chemical Substances (RTECS), the Integrated Risk Information System (IRIS) and the Hazardous Substances Data Bank (HSDB). This allowed us to determine if any pertinent literature had been omitted in the RCD. We would be happy to share the assembled information. In order to assist you in revising the draft RCD, we have cited selected published works at the end of this report that may be worth considering in your overall evaluation.

Assessment of Cancer Risks

In the draft RCD (Volume I), the evaluation of potential oncogenicity from exposure to naled was based on three currently available chronic gavage studies (in rats, mice and dogs) and on genotoxicity tests. There were no oncogenic effects reported in the gavage studies in mice (Charles River CD-1) and dogs (Beagles).

In the rat study (Sprague-Dawley) the oncogenic findings were noted in both males and females. In male rats, the findings consisted of a slightly increased incidence of mammary adenocarcinomas at 2 (1/49) and 10 mg/kg-day (2/49). However, only the trend was statistically significant at $p \leq 0.05$ based on a dose-weighted chi-square trend test. There were a variety of mammary tumors observed in female rats (fibroadenomas, adenomas and adenocarcinomas). The results in female rats were determined in the draft RCD as "not related to treatment since they were higher in the controls than those in the treated groups." This statement appears to be correct for adenomas and adenocarcinomas but not for fibroadenomas where the incidence of tumors was higher in all treated groups in comparison with control animals (naled RCD, Volume I, Table 9, page 32). Overall, the rat study was considered to be negative in the draft RCD.

The lack of strong evidence of oncogenic effects from exposure to naled is in contrast to the carcinogenic effects produced in studies with dichlorvos (DDVP), the main toxicologically active metabolite and degradation product of naled. Oncogenic effects were shown in two long-term gavage studies in rats and mice (DPR, 1994). Tumors observed in rats (F344/N) included: pancreatic adenomas (statistically significant in males), mononuclear leukemia (statistically significant in males, clear dose-response trend in females), and mammary gland tumors (carcinoma, fibroadenoma, and adenoma) in females (statistically significant at the dose level of 2.9 mg/kg-day). Oncogenic changes produced in mice (B6C3F1) consisted of forestomach tumors such as squamous papillomas and squamous cell carcinomas (statistically significant in males and females) (DPR, 1994).

According to the draft RCD for naled, it has been concluded that only mononuclear leukemia is clearly related to DDVP exposure (Volume I, page 48). In the draft RCD, the findings of mammary gland fibroadenomas were considered equivocal evidence for oncogenicity, and the increased incidence of pancreatic adenomas following DDVP exposure was considered to be related to the use of corn oil as the vehicle.

According to the evaluation of the available tests on gene mutations, chromosomal aberrations and DNA effects provided in the draft RCD, naled was not found to be genotoxic in either *in vitro* or *in vivo* studies (naled RCD, Volume I, page 36). We find the results of these studies to be equivocal. Some of the results suggest "conflicting evidence for mutagenicity" while results of other studies provide some evidence for positive responses. The latter were disregarded in the draft RCD because "there was insufficient information presented for evaluation." In some cases, the observed positive responses were not statistically significant and therefore the results were considered to be negative. In considering the database as a whole, however, we conclude that the combination of the positive and the equivocal studies provides some evidence that naled is genotoxic. Consequently, there is still some uncertainty regarding the genotoxicity of naled.

In contrast, DDVP was genotoxic in some *in vitro* systems, including assays with *Salmonella TA 100* strain and *Schizosaccharomyces pombe*, mouse lymphoma forward mutation assay, and unscheduled DNA synthesis assay using human epithelial cells. DDVP was not genotoxic in the micronucleus, dominant lethal, *in vivo* chromosomal aberrations, and *in vivo* sister chromatid exchange assays (IRIS, 1998).

DDVP is currently under Special Review by U.S. EPA. In 1989, the Scientific Advisory Board of U.S. EPA recommended that the DDVP oncogenicity classification be changed from a B2 carcinogen to a C carcinogen. Most of the food tolerances for DDVP have been revoked. In 1993 the registrants of DDVP in California voluntarily canceled its use on fresh vegetables.

Our review of the data presented in the draft RCD for naled indicates that the issue of the potential carcinogenicity of naled should be more thoroughly addressed. Oncogenicity data on DDVP should not be disregarded in the overall evaluation of potential oncogenicity for naled. The carcinogenicity of the major metabolite of naled, DDVP, represents an important uncertainty regarding the carcinogenicity of naled. We understand the scientific challenge for risk assessment

presented by the limited evidence of carcinogenicity provided by the bioassays of naled coupled with the clearly positive outcome from bioassays of its major metabolite DDVP.

We recommend that the naled RCD more broadly address the uncertainties in identifying oncogenic hazard and characterizing cancer risk from exposure to naled. Comparison of the protocols and conditions of oncogenicity studies performed for DDVP and naled would be useful. Issues like the dose-equivalent of DDVP from naled administration compared to the DDVP dose in the positive cancer assays, different laboratory conditions and different strains of animals used to assess oncogenic potential of naled and DDVP may contribute to understanding the different toxicological outcomes for these two compounds. It should be noted that mammary tumors were produced in the oncogenicity study with naled (Sprague-Dawley rats) as well as in the oncogenicity study with DDVP (F344/N rats). It would also be useful to analyze more thoroughly the pharmacokinetic behavior of naled under different experimental conditions. In addition, separate exposure data for DDVP derived from naled are available to calculate DDVP-related cancer risk from naled use.

In summary, we conclude that for risk assessment purposes, there is limited evidence for the carcinogenicity of naled in bioassays. This comes from direct evidence from the development of rare mammary tumors in male rats exposed to naled and the supporting evidence from the carcinogenicity of DDVP, the primary metabolite of naled, which caused an increase in the incidence of mammary tumors in a second strain of rats. At present, the difference between the stronger evidence of carcinogenicity of the primary metabolite and the relatively limited evidence of carcinogenicity for the parent compound has no scientific explanation and should be investigated further before concern over the carcinogenicity of naled can be dismissed. In the interim, since DDVP is the major metabolite of naled, we recommend that naled be considered a potential carcinogen and the cancer risk from exposures to DDVP resulting from naled exposures be assessed before finalizing the naled RCD. This assessment should also consider residues of DDVP on agricultural commodities following naled applications (e.g., consumer exposure) and traces of DDVP as a degradation product or as a metabolite of naled (e.g., occupational exposure).

Weight-of-Evidence for Carcinogenicity

The issue of potential carcinogenicity from exposure to naled deserves special attention because of the contrasting results from oncogenicity testing of naled and its major metabolite DDVP. In addition to the suggestions presented above, to better characterize the uncertainties regarding naled carcinogenicity, we recommend that the structure-activity relationship also be addressed in the RCD for naled and its breakdown products. Consequently it should be noted that DDVP is structurally related to dichloropropene (a probable human carcinogen), which causes forestomach squamous cell tumors in rats and mice, lung tumors in mice and neoplastic nodules in the livers of rats (IRIS, 1998; HSDB, 1998).

The discussion of the weight-of-evidence for potential carcinogenicity from naled can be broadened by addressing the issue of carcinogenic effects caused by another organophosphorous compound, trichlorfon. DDVP is also a major metabolite and breakdown product of trichlorfon.

It is noteworthy that trichlorfon (tested as a parent compound) caused numerous oncogenic effects such as renal tubular adenomas, alveolar/bronchiolar adenomas and mononuclear cell leukemia in Fisher 344 rats. The latter carcinogenic effect is unequivocally related to the exposure of rats to DDVP (DPR, 1995).

Another metabolite of naled with clear evidence for carcinogenicity (in mice) is dichloroacetic acid (DCAA) (DeAngelo *et al.*, 1991; 1996). U.S. EPA considers DCAA as a probable human carcinogen (B2). This evaluation is based on an increased incidence of hepatocellular adenomas and carcinomas in male and female mice (B6C3F1). Hyperplastic liver nodules, which are expected to progress into hepatocellular adenomas and carcinomas, were increased in both mice and rats.

Choice of Critical NOELs for Risk Assessment

The draft RCD provides assessment of health risk only from exposures to naled under acute and chronic conditions. We support the choice of the studies for these evaluations. However we recommend that further explanation be provided in the RCD as to why these studies are the most appropriate for risk assessment.

The acute exposure assessment is based on an "estimated no-effect-level (ENEL)" of 2.5 mg/kg-day calculated from a lowest-observed-effect-level (LOEL) of 25 mg/kg-day established in an acute oral study in rats. The LOEL was divided by a default factor of 10 for the extrapolation of the no-observed-effect-level (NOEL) from an LOEL. The LOEL is based on tremors, exophthalmus and "other effects" (naled RCD, Volume I, page 67, "Risk Appraisal" under "Acute Toxicity"). It is not clear what are the "other effects" because they are not listed. The subject study is described in Volume I, page 41, paragraph 3, under "Neurotoxicity." However there is no indication there that this study was chosen for risk assessment. It is also difficult to quickly identify this study while reading the section on "Risk Appraisal" (page 67). We recommend that references to the study being discussed be inserted in the appropriate sections.

We also recommend that references to the chronic studies chosen as a basis for risk assessment be inserted in the appropriate sections. These were chronic gavage studies in rats and dogs in which the NOEL is 0.2 mg/kg-day established for brain ChE inhibition.

Seasonal Exposure Assessment

The draft naled RCD concludes that there are no seasonal occupational or residential exposures (Volume I, page 47, last paragraph), and no seasonal dietary exposure. We agree that there are no dietary or residential seasonal exposures. However, in the light of the broad agricultural use of naled on many commodities, especially cotton, estimates of seasonal occupational exposures is still important. We recommend that the RCD (Volumes I and II) be revised to include such an estimate.

Uncertainty Factor for Children's Exposures

The draft naled RCD (Volume I, page 69) addresses the requirements of the Food Quality Protection Act of 1996 (FQPA). This legislation mandates U.S. EPA to ensure that tolerances for pesticides on food are safe for children. Specific requirements include: 1) the use of an extra 10-fold safety factor to account for potential pre- and post-natal developmental toxicity and the completeness of the data unless U.S. EPA determines, based on reliable data, that a different margin of exposure would be safe, and 2) consideration of the available information on aggregate exposure from all nonoccupational sources, the effects of cumulative exposure to the pesticide and other substances with a mechanism of toxicity in common, the effects of *in utero* exposure, and the potential for endocrine disrupting effects.

In the draft RCD, an additional uncertainty factor to account for pre- and postnatal developmental toxicity and the completeness of the database was not incorporated. The draft document states that "The database for naled was complete for the evaluation of potential pre- and post-natal sensitivity from exposure" and that "There was no evidence of increased pre- and post-natal sensitivity from developmental or reproductive toxicity." We recommend reevaluation of the potential pre- and post-natal toxicity to naled and the completeness of the database for the following reasons:

1) Existing testing requirements do not specifically (and/or adequately) address pre- and postnatal sensitivity. The existing developmental and reproductive toxicity studies do not completely nor specifically test for related toxicity endpoints. This especially applies to the lack of testing for potential neurobehavioral (postnatal) effects which may be of importance for chemicals affecting the central nervous system.

2) There was a decrease in fetal body weight in a pilot rabbit study at a NOEL of 2 mg/kg-day while the acute NOEL for maternal toxicity was established at a higher level of 10 mg/kg-day (naled RCD, Volume I, page 40).

3) DDVP, the major metabolite of naled (and trichlorfon) was shown to cause severe reduction in brain weight in guinea pig offspring (examined at birth) when administered between day 42 and 46 of gestation (DeAngelo *et al.* 1991).

Based on the evidence of pre- and post-natal toxicity and the existing level of uncertainty regarding the adequacy of the testing requirements for pre- and postnatal toxicity, we recommend that the use of an additional uncertainty factor to account for pre- and postnatal sensitivity be reconsidered.

Exposure Assessment

The draft RCD demonstrates potential for excess exposure to naled and its metabolite DDVP under several conditions. However, the draft exposure assessment (Volume II) does not account for the higher acute and subchronic toxicity of DDVP in occupational exposures to naled even though separate measurements of naled and DDVP are available. Because DDVP is four to

five times more acutely toxic than naled, exposures to the two chemicals should not have been considered equivalent, and simply added, in calculating exposures to grape harvesters. Because the same data were used in estimating exposures for other conditions, such as greenhouse work, combined toxicity calculations [naled + (5 x DDVP)] would also have been appropriate in these cases.

The draft RCD provides only limited discussion of the range and distribution of potential occupational exposures. The draft exposure assessment states that "the values assumed for the application rate and for the daily usage were already at their (practical) maximum" (Volume II, page 24). This is an inadequate scientific explanation. At the maximal application rate and practical maximum daily use, there will still be a range of exposures due to differences in work practices, as shown in every exposure study.

The draft document also states "Because of the great variability inherent in the PHED data, the upper-end values would be unrealistically high to use...." This statement is not scientifically justified. Information on page six of the draft exposure assessment indicates that there have been exposures in California associated with systemic effects and low cholinesterase levels as would be expected from upper-bound exposures. The data indicate 79 cases of systemic effects out of 137 total cases of naled illness or injury reports between 1982 and 1995. Ten of these cases reported low ChE levels. We recommend that the risk characterization attempt to associate these effects (and the probability of such effects) with exposures and the use practices as a critical part of the total evaluation.

SPECIFIC COMMENTS

Risk Characterization Document, Volume I

Page 1, paragraph 4. The statement that "Under some environmental conditions, naled may be completely metabolized to carbon dioxide" and the statement on page 7, paragraph 1 "Depending on the environmental conditions, naled may be completely metabolized to carbon dioxide" should be supported by providing examples of such "conditions." We are not clear how this would occur. Bromochlorophosphates cannot be transmuted to CO_2. The use of the word "metabolized" does not appear to be appropriate in conjunction with "environmental conditions."

Page 2, paragraph 4. Typographical error. The word "decreased" should be changed to "decrease."

Page 7. The section on "Environmental Fate" might be easier to follow if it were reorganized to separately address terrestrial fate, aquatic fate and atmospheric fate. A conclusion regarding the potential for ground water contamination should be stated in this section.

Page 17, paragraph 1. Chemical name of temephos [(phosphorothioic acid, O, O'-(thiodi-4,1-phenylene) O, O, O' O'-tetramethyl ester] should be provided.

Page 21, second paragraph. The concentration of naled in the formulation reported here appears to be very low for a 91.5% pure mix (compare with other formulations described in this section). One possibility is that it should be 1.14 mg/L rather than 1.14 μg/L. If this is true, then the conclusion that there were high levels of DDVP (compared with other studies) and the study is only supplemental appears to be invalid.

Page 50, last paragraph. The approach of not using pesticide residue levels discovered to be over tolerance in dietary risk calculations is not mathematically or conceptually valid. Without adequate justification to support a different method, all data should be used. For naled, if no over-tolerance residues occurred it should be specified somewhere in the document. This approach has also caused an additional problem on page 53, second paragraph, where it is stated that "The TEF was not applied to the tolerance since the tolerance was the maximum naled and DDVP residues allowed on the commodities." If the data indicate a mixture of naled and DDVP in the product, then the evaluation should reflect this.

Pages 54-55, Table 17. Listing or referring to DDVP tolerances would be useful here, since both naled and DDVP levels are used in the calculations.

Page 58, first paragraph. We agree that using the tolerance level for estimating cancer risk for carcinogens in foods would overestimate risk. Nevertheless, this is not in itself a reason for not including an estimate of cancer risk from dietary exposures in the naled RCD. Instead, more appropriate residue level estimates should be utilized for calculating a lifetime cancer risk for DDVP derived from naled. As above, we recommend including a cancer risk assessment in the revised RCD for naled.

Page 69, first paragraph. The draft RCD states that the uncertainty factors of 10 "assume that the average human is 10 times more sensitive...than the most sensitive experimental animal, and that a sensitive individual is 10 times more susceptible than an average individual." The scientific rationale for use of these defaults in risk assessment could be stated more clearly. Use of a factor of 10 for intra-species extrapolation assumes that the average human may be up to 10 times more sensitive than the average animal in the most sensitive species or strain which happens to have been tested. Also, a sensitive individual may be up to 10 times more sensitive than an average individual. It is the uncertainty in the database and methods that supports the use of these factors, not the assumption that humans are in fact more sensitive, nor that there are individuals 10 times more sensitive than the average. The most important aspect of this difference in interpretation is that additional data may lead to modification (increasing or decreasing) of these factors when appropriate data are available. We recommend rewriting this paragraph.

Pages 70, Section V.E.3. It is appropriate that the draft RCD acknowledges that while cumulative exposures to organophosphates (which have similar mechanisms of action) should be considered, the methodology for this is still under development. Simultaneous exposure to chemicals with the same mechanism of action provides support for the need to include an additional uncertainty factor to protect infants and children.

Page 72, Section VI.B. As stated in the draft RCD, the exposure of infants at the tolerance level represents an inadequate margin of exposure (MOE) with several MOEs reported to be in the range of 51 to 56, and possibly lower if different assumptions and approaches were used. We recommend that the RCD include further discussion regarding the impact of co-exposures to other organophosphate pesticides that would further decrease this MOE, resulting in a finite probability of cholinergic effects when such potent organophosphate cholinesterase inhibitors are widespread in our food supply.

Risk Characterization Document, Volume II

Page 4, pesticide usage. It should be explicitly stated that pesticide usage estimates do not include household uses of naled, including use in animal flea and tick collars. The present wording of "79% of the total annual usage was on cotton" should be revised to "79% of the reportable usage was on cotton." No estimates are available for total usage in the 12 registered flea and tick collars, although this may represent a significant portion of total population exposures. We recommend rewording this paragraph to include a statement to this effect.

Page 5. The title of Table 3 "Raw agricultural commodities with the 8 highest (for the majority years) percent usage from 1991 through 1995" is confusing, and should be renamed for clarity. It is unclear whether the title refers to the highest usage of naled in pounds as a percent of total naled use by year, or the percent by total acres treated, or the percent of the individual crops treated. If this is based on use by pounds, it appears that for the years 1993 through 1995 use on grapes decreased five-fold, orange and safflower use did not change, use on broccoli doubled and use on cotton increased 20-fold. The interpretation of use is critical to further the discussions of population exposures and risks. If true, it appears that high-exposure use on grapes is decreasing, while the use on cotton, a low exposure use, is increasing. It would be reasonable to discuss this issue in the revised RCD.

Page 7. For naled, the default dermal absorption rate of 50% is appropriate in the absence of data. Because of its relatively high vapor pressure, the actual level of dermal absorption might be lower than 50%.

Page 11. The estimate of total naled exposure of human volunteers based on their urinary excretion of dimethyl phosphate (DMP) "within 3 hours after the application" is not fully justified in the draft document. For example, no scientific information was provided on the proportion of exposure by inhalation compared to dermal absorption, which would influence the duration of the total exposure to naled, the rate of systemic absorption of naled, and the rate of its metabolism and excretion. The calculation of total exposure based on two-hour excretion of the chloroethyl metabolite (the leaving group) in rats after a bolus oral exposure, compared to the excretion of DMP (the moiety which binds to cholinesterase) after a mixed-route human exposure for an unknown duration, is not justifiable. The apparent assumption in the first paragraph that the concentration of DMP in the urine collected "within 3 hours" applies to the entire day's urine volume is similarly not supportable. Furthermore, the last paragraph on this page identifies some uncertainties in the human exposure data that appear to invalidate the data for use in risk assessment. We recommend deleting the discussion.

Pages 14-18. Exposure estimates of field workers are based on experiments in grapes. The assumption that crops such as cotton, strawberries and citrus trees achieve the same foliage residue levels as grapes does not appear to be appropriate considering the different amounts of foliage for the different crops. We recommend presenting data or at least including a discussion of residue level data obtained from other pesticide applications to provide better estimates and to support the calculations. In addition, adding the exposures to naled and DDVP together without correction for the greater toxicity of DDVP is not scientifically justified given the availability of data. If the respective potencies are accounted for in the calculation, the combined effective naled exposure is significantly greater than what is presented in the draft document. We recommend correcting the exposure estimates based on a relative potency consideration.

Page 22, fourth paragraph. The assumption that an individual would be exposed to 100% of the active ingredient lost from an animal collar over 90 days (presumably in normal use) probably overestimates risks. Obtaining measurements of residues coming off during handling would help reduce the uncertainty in this assumption. Acknowledgment of this in the revised exposure assessment would be helpful if the data cannot be easily obtained.

Page 23, next to last paragraph. We recommend providing additional discussion in the revised exposure assessment in support of the assumption that it is appropriate to use exposure estimates from backpack sprayers for those who treat sewage systems via injection.

Page 24, third paragraph. The use of maximal application rates (pounds/acre) and amounts of daily usage (acres/day) does not constitute an adequate evaluation of the maximum likely exposures. Under experimental conditions, measured exposures typically vary over 100-fold. Exposure estimates that do not incorporate the range of likely exposures do not provide adequate perspective on why some applicators become symptomatic, while others do not. We recommend including this information in the revised exposure assessment to better document the types of pesticides and application methods that constitute worker hazards.

Page 24, last paragraph. It is stated that "Adverse effects occur only when plasma levels in the target organ exceed a critical level." This statement generally refers to a chemical that acts in a reversible manner; it is less relevant for a kinetically irreversible mechanism of action such as the organophosphate acetylcholinesterase (AChE) inhibitors. Effects of the di-O-methyl organophosphates like naled are cumulative over at least a couple of days. One estimate is that spontaneous reactivation of di-O-methyl-phosphorylated AChE occurs at a rate of about 1% per hour. Resynthesis of AChE occurs at different rates for different tissues, but may be as much as 10% per day in some neuronal reservoirs. The sum of reactivation, resynthesis, and acute tolerance determines most of the cumulative toxicity potential of organophosphate exposures (metabolic changes with repeated exposures are also important for some organophosphates). The relatively slow recovery rate is responsible for the fact that the acute NOEL of naled is 2.5 mg/kg-day, while the chronic NOEL is much lower at 0.2 mg/kg-day. Based on these considerations, we conclude that the entire discussion in this last paragraph on page 24 is not justified and should be deleted.

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