Findings of the Scientific Review Panel on
Evaluation of DEF as a Toxic Air Contaminant
April 13, 1999

Pursuant to Food and Agricultural Code (FAC) section §14022 and §14023, the Scientific Review Panel (SRP/Panel) has reviewed the report, "*Evaluation of S,S,S-tributyl phosphorotrithioate (DEF) as a Toxic Air Contaminant,*" prepared by the Department of Pesticide Regulation (DPR) describing the public exposure to and health effects of DEF. The Panel members reviewed the public comments and the reviews of the Office of Environmental Health Hazard Assessment (OEHHA) and the Air Resources Board.

Furthermore, OEHHA has reviewed the report on the health effects of DEF for the purposes of considering the identification of DEF as a Toxic Air Contaminant. As part of its statutory responsibility, OEHHA has prepared findings on the health effects of DEF which are to be included as part of the DPR report.

Based on the review and evaluation of DEF, provided in the DEF report, the Panel makes the following findings pursuant to FAC §14023:

Environmental Fate and Exposure

1. DEF is applied to cotton from September through October in the San Joaquin Valley and from August through September in the Imperial Valley. The duration of DEF use in both locations is approximately 60 days, corresponding to the cotton defoliation season.

2. Over the past ten years between 750,000 to 1,000,000 pounds of DEF per year were applied in California.

3. DEF is transformed in the environment, at least in part, to n-butyl mercaptan (nBM) and n-butyl disulfide (nBD). Therefore, the health effects associated with the use of DEF include the direct effects of DEF (through its active metabolite) and may also include the effects of nBM and nBD.

4. DPR reviewed all available literature on ambient air levels of DEF as of August 1998. The two most relevant sources to characterize ambient air exposures came from monitoring studies performed in Fresno (Seiber *et al.*, 1988) and Kern (Kilgore *et al.*, 1984) Counties during the cotton defoliation season when DEF was applied. The highest levels of DEF in ambient air were detected in Fresno County. Rural ambient air levels of DEF evaluated at four locations in towns in Fresno County near cotton fields ranged from nondetectable (detection limit 1.1 ng/m^3 or 0.09 ppt) to 548 ng/m^3 (corrected for trapping efficiency). The mean levels ranged from 43.9 ng/m^3 to 182 ng/m^3.

5. The oral absorption rate of DEF in rats was estimated to be 70%; inhalation absorption data is unavailable and was therefore conservatively assumed to be 100%.

6. After DEF administration by the oral route, significant amounts of nBM are formed, probably both by acid hydrolysis in the gut and by liver metabolism. The report did not identify the relative proportion of DEF oxidation to the active cholinesterase (ChE)-inhibited moiety, versus hydrolysis to S,S-dibutyl phosphorothioate and nBM from oral or inhalation routes. Therefore, toxic effects may differ by route of administration.

7. For the above reasons the health effects of nBM have also been evaluated in the DEF report. No toxicity data is available for nBD.

Health Effects

Animal Studies

8. Acute and subchronic exposures to DEF produce cholinergic effects (including lacrimation, salivation, hypothermia and neurological effects, depending on dose) by inhibiting ChE.

9. Acute and subchronic exposures to DEF by gavage or inhalation in hens produces a delayed neuropathy of a mixed type, including an organophosphate-induced delayed neuropathy (OPIDN).

10. Acute inhalation exposures to nBM can result in respiratory irritation, central nervous system (CNS) depression and lung, renal, and liver damage.

11. Chronic exposure to DEF can result in small intestine damage, spleen hematopoiesis, hematological changes, cholinergic effects, and ocular damage (including retinal and ocular nerve atrophy and corneal opacity).

12. DEF is a potential reproductive toxicant in rats; oral exposure induced reductions in fertility, birth and viability indices, increased gestation length, reduced pup weight, and clinical signs and gross pathological lesions in pups.

13. nBM is a potential developmental toxin in mice; inhalation exposures result in significantly increased post-implantation losses and fetal malformations.

14. DEF oral administration produced significantly increased incidences of the following tumor types in mice: small intestine adenocarcinomas and hepatic hemangiosarcomas in males, and lung adenomas/adenocarcinomas in females. A weight-of-evidence analysis for carcinogenicity was not conducted, but the potential cancer potency and risk were evaluated.

Humans

15. Symptoms reported by people potentially exposed to DEF through occupational exposure or through ambient air near DEF-sprayed cotton fields included ocular and respiratory irritation (e.g., wheezing, coughing, nasal and chest congestion) and cholinergic effects consistent with acetylcholinesterase inhibition (e.g., diarrhea, muscle weakness, miosis, dizziness).

16. One case report describes the development of findings consistent with OPIDN following accidental exposure to merphos (S,S,S-tributyl phosphororithioite), which is readily converted to DEF upon air exposure.

17. One case describes occupational exposure to DEF resulting in a reduction of neuropathy target esterase (NTE) activity in lymphocytes. The inhibition of NTE in sensitive species is a biomarker that correlates with the induction of OPIDN.

Potency and Range of Risk to Humans

18., The report identified no-observed-adverse-effect levels (NOAEL). Since the report provides a basis for risk management, the inclusion of the NOAEL provides information for risk mitigation. It is important to note that NOAELs are based on limited existing knowledge and that adverse effects not yet measured may occur at lower levels of exposures. The report identified an acute air NOAEL of 2.4 mg/m^3 (0.6 mg/kg-day) for DEF based on blood ChE inhibition and a NOAEL of 12.2 mg/m^3 (2.9 mg/kg-day) for DEF based on clinical signs (e.g., bradypnea, irregular breathing, increased startle response) in rats during the first three days of exposure of a 90-day inhalation study. The NOAEL was adjusted for the respiratory differences between rats and humans; since children had the highest respiratory rate for humans relative to their body weight, their respiratory rate was used for humans. The adjusted NOAEL based on blood ChE inhibition is 0.88 mg/m^3, assuming a 24-hour respiratory rate of 0.68 m^3/kg for a 6-year old child.

19. The report identified a subchronic NOAEL of 2.4 mg/m^3 (0.6 mg/kg-day) for DEF based on blood ChE inhibition and an NOAEL of 12.2 mg/m^3 (2.9 mg/kg-day) for DEF based on clinical signs noted for the acute NOAEL, plus brain ChE inhibition, impaired retinal function, hematological changes, and adverse adrenal changes (increased weight, fatty droplets) in a 90-day rat inhalation study. The adjusted NOAEL (as noted for the acute NOAEL) based on blood ChE inhibition is 0.88 mg/m^3, assuming a 24-hour respiratory rate of 0.68 m^3/kg for a 6-year old child.

20. An "air concentration level" (equivalent in this usage to an OEHHA reference exposure level (REL)) of 8.8 ug/m^3 (0.68 ppb) was calculated for acute and seasonal exposure based on the acute and subchronic NOAELs (blood cholinesterase inhibition) listed above. The NOAEL value is the air concentration below which there is no anticipated human health risk. It incorporates a 100-fold uncertainty factor to address potentially increased sensitivity of humans and variability of response between humans.

21. The report estimated margins of exposure (MOEs) from Fresno and Kern Counties using monitoring data and the NOAEL listed above. The acute and seasonal MOEs from Fresno County, the county of greatest measured exposure, based on the NOAEL (cholinesterase inhibition) for children ranged from 2,000 to 4,900 and for adult males the values ranged from 4,800 to 12,000.

22. Cancer potency factors were calculated for DEF based on the incidence of liver hemangiosarcomas in male mice after oral DEF exposure; the potency ranged from 4.7×10^{-2} (maximum likelihood estimate (MLE)) to 8.4×10^{-2} (upper 95% confidence level (95% UCL) $(mg/kg\text{-}day)^{-1}$ after correction for a 70% absorption factor. The corresponding unit risk estimates are 9.24×10^{-6} $(ug/m^3)^{-1}$ for the MLE and 1.65×10^{-5} $(ug/m^3)^{-1}$ for the 95% UCL.

23. The report estimated a cancer risk due to a lifetime exposure to DEF in ambient air in Fresno County which ranged from 3.9×10^{-7} (MLE) to 7.1×10^{-7} (95% UCL). The corresponding estimated cancer risk for Kern County ranged from 7.5×10^{-8} (MLE) to 1.3×10^{-7} (95% UCL).

24. The report calculated an acute NOAEL for nBM of 10 ppm (37 mg/m^3; 17 mg/kg-day) from developmental toxicity observed in a mouse inhalation study based on increased mortalities, reduced body weight gain, and clinical signs in the dams (unkempt appearance, lethargy, red/brown perianal staining), increased post-implantation losses, and fetal malformations. An adjusted NOAEL of 25 mg/m^3 can be calculated from the animal NOAEL assuming a 24-hour respiratory rate of 0.68 m^3/kg-day (6-year old child). Therefore, an acute air concentration level for nBM of 250 ug/m^3 (67.8 ppb) can then be calculated from the adjusted NOAEL using a standard uncertainty factor of 100.

Uncertainties or Other Relevant Information

25. The report identified a subchronic NOAEL of 2.4 mg/m^3 (0.6 mg/kg-day) for DEF based on blood ChE inhibition in a 90-day rat inhalation study. However, the report noted NOAELs from a 90-day hen feeding study and a rat toxicity study of 0.1 mg/kg-day (ataxia) and 0.4 mg/kg-day (brain ChE inhibition), respectively.

26. While the hen feeding study has a 6-fold lower NOAEL on a mg/kg-day basis, there are some uncertainties in using it to establish an inhalation NOAEL. First, a cross-route extrapolation needs to be performed. Second, this study suggests an underestimation of risk using the 90-day rat inhalation study. There is considerable uncertainty in quantifying and applying the hen study for inhalation exposure. The SRP requests DPR and OEHHA to evaluate the hen delayed-neurotoxicity model and determine how it may be used to perform quantitative risk assessments.

27. The NOAEL of 0.4 mg/kg-day based on brain cholinesterase inhibition for the rat oral toxicity study is close to the NOAEL of 0.6 mg/kg-day based on blood cholinesterase inhibition for the rat inhalation study.

28. The community health impact of nBM and nBD from DEF usage is uncertain. For these two compounds there is only acute toxicological information available for nBM. Evaluation of the relationship between the odor thresholds and the "air concentration levels" if they were available, could assist in assessing the toxicologic impact of these substances.

29. However, as indicated in the reports, the available toxicity and monitoring data for nBM is insufficient for the purposes of adequately characterizing the potential health risk associated with nBM exposure and determining margins of exposure (if any) associated with nBM exposures.

Conclusions

30. The report estimated a cancer risk due to a lifetime exposure to DEF in ambient air in Fresno County ranged from 3.9×10^{-7} (MLE) to 7.1×10^{-7} (95% UCL). The corresponding estimated cancer risk for Kern County ranged from 7.5×10^{-8} (MLE) to 1.3×10^{-7} (95% UCL).

31. DPR regulations (California Code of Regulations, Title 3, Section 6890(b)) specify criteria for identifying pesticides with adverse health effects that do not have thresholds as toxic air contaminants. For such pesticides, if there are concentrations in air that exceed levels resulting in more than a ten-fold lower risk than a level determined by the Director to be a negligible risk, then the pesticide shall be identified as a toxic air contaminant.

32. For non-threshold toxic endpoints, one in a million risk typically represents the negligible risk standard. If the Director determines that one in a million risk is a negligible risk for pesticides that do not have thresholds for adverse health effects, then according to criteria established in DPR regulations, pesticides with risks greater than one in ten million (10^{-7}) should be identified as toxic air contaminants.

33. The Panel, after careful review of the draft version of the DPR report, "*Evaluation of S,S,S-tributyl Phosphorotrithioate (DEF) as a Toxic Air Contaminant*," as well as the scientific procedures and methods used to support the data, the data itself, and the conclusions and assessments on which the report is based, finds this report with the changes, identified by the Panel, is based upon sound scientific knowledge, methods, and practices and represents a balanced assessment of our current scientific understanding.

34. For these reasons, we agree with the science presented in the report, and recommend the Director of DPR identify DEF as a toxic air contaminant.

I certify that the above are the
Findings adopted by the
Scientific Review Panel on April 13, 1999.

John R. Froines

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