Dichlorvos (DDVP)

ADDENDUM[1]

to Risk Characterization Document

November 4, 1997

I. SUMMARY

INTRODUCTION

This addendum reevaluated the risk assessment of dichlorvos (DDVP) because of submitted human oral toxicity studies. In the 1996 Risk Characterization Document (RCD), the margins of exposure (MOE) were based on experimental animals. Most of the MOEs for workers and residents were below the conventional benchmark for human health protection.

TOXICOLOGY PROFILE

In the single dose studies, DDVP (1.0 mg/kg, highest dose tested) given in capsules to volunteers resulted in statistically significant inhibition (10%) of erythrocyte cholinesterase (ChE). Erythrocyte ChE inhibition was also inhibited (5-10%) at 0.5 mg/kg DDVP. In another study with volunteers given 0.3 mg/kg/day DDVP for 15 days, the erythrocyte ChE activity was significantly inhibited (15-30%) during and after exposure. At a lower dose of 0.1 mg/kg/day for 21 days, the erythrocyte ChE inhibition was 10-15% during the exposure.

RISK ASSESSMENT

The critical NOEL for acute oral exposure was revised to 0.5 mg/kg based on the human study. Because of uncertainties in route-to-route and time extrapolations, the critical NOELs for chronic dietary exposures and occupational and residential exposures remained the same as in the 1996 RCD. The margins of exposure for acute and chronic dietary exposures remained higher than the benchmark considered protective of human health. However, most of the occupational and residential exposures as well as the lifetime dietary exposures remained below the benchmarks.

RISK APPRAISAL

Depending on the endpoint and exposure duration, there were differences between humans and rats in the sensitivity to the toxicity of DDVP. Therefore, using an interspecies extrapolation factor was appropriate when the risk assessment was based on experimental animal studies. An additional uncertainty factor was not needed to account for the potential increased sensitivities of infants and children.

TOLERANCE ASSESSMENT

The MOEs for exposure to residue levels at tolerances remained the same.

CONCLUSIONS

This addendum did not change the conclusions in the 1996 RCD. The MOEs for acute and chronic dietary exposure remained above the benchmark considered sufficient for the protection of human health. For most of the non-dietary exposure scenarios, the MOEs or oncogenic risks did not meet the benchmarks considered protective of human health.

II. INTRODUCTION

The 1996 Risk Characterization Document (RCD) detailed the risks associated with the use of dichlorvos (DDVP) in California and was based on animal studies (Lim *et al.*, 1996). Most of the occupational and residential scenarios resulted in MOEs, previously referred to as margins of safety (MOS), of less than 100, the value conventionally considered protective of human health. Consequently, a mitigation process was initiated in the Department of Pesticide Regulation (DPR) to reduce exposure. In March 1997, new acute and subchronic oral toxicity studies in humans were submitted to DPR. In addition, the 1996 Quality Protection Act mandated specific findings on the potential increased sensitivities by infants and children. This addendum reassessed the risks, taking into consideration the human studies and the mandate under the Food Quality Protection Act.

III. TOXICOLOGY PROFILE

A. TOXICOLOGY

Three oral toxicity studies in humans (Caucasian male, fasted, healthy volunteers) were conducted (Stonard, 1997; Gledhill, 1997 a, b, and c). In each study, blood samples were collected before and after dosing at scheduled intervals to measure erythrocyte cholinesterase (ChE) activity. Analysis of the urine for dimethyl phosphate, a metabolite of DDVP, was not successful. Body temperature was also taken and no changes were reported.   Twenty-four hours after each dose, each volunteer was interviewed for the occurrence of symptoms such as anxiety/ restlessness, dizziness, headache, nausea/ vomiting, salivation/ sweating, diarrhea, abdominal colic, and paralysis/ fits/ unconsciousness.

The first study consisted of two phases and the volunteers (age 20-32 years, weight 66-89 kg) were given DDVP (97.7% pure) in corn oil in capsules in each phase (Gledhill, 1997a). In Phase I, four volunteers were given a single oral dose of DDVP (35 mg/person or 0.5 mg/kg for a 70 kg male). Erythrocyte cholinesterase inhibition was determined on days 1, 3, 5 and 7 or 8 days of the experiment. Two weeks after the first dose, these volunteers and 2 new volunteers were given the same dose again. In Phase II, the same volunteers from Phase I were dosed with DDVP (21 mg/person; 0.3 mg/kg) for 12 (2 men) or 15 days (4 men). Erythrocyte cholinesterase inhibition was determined on days 3, 5, 8, 10, 12, 15, 17, 19, 22, and 24 days of the experiment.

In Phase I, a single dose of DDVP (0.5 mg/kg) resulted in a statistically significant ($p < 0.05$) decrease (90%-95% of pre-dose level) in the group mean erythrocyte ChE activity. In Phase II, the group mean erythrocyte ChE activity was significantly ($p < 0.01$) decreased from day 5 to day 33. The activity was 85% and 81%, respectively, of pre-dose levels on days 5 and 33. The maximal inhibition was 60% of the predose level on day 22, 7-10 days after the last dose. On day 54, erythrocyte ChE activity was 91% of pre-dose level. No treatment-related clinical signs were reported in either Phase I or Phase II.

In the second study, six volunteers (age 20-30 years, weight 67-80 kg) were given a higher single dose of DDVP (98% pure; 70 mg/person or 1.0 mg/kg for a 70 kg male) in capsules (Gledhill, 1997b). Erythrocyte cholinesterase inhibition was determined on days 1, 3, 5 or 6, 7 and 14 days of the experiment. Compared to pre-dose levels, the group mean erythrocyte ChE activity was significantly (p<0.01) reduced (about 10%) on days 5, 7, and 14. No treatment-related clinical signs were observed.

The third study was a single blind, randomized, placebo controlled multiple dose study in 9 volunteers (age 19-34 years, weight 61-90 kg) using a lower dose than that in Phase II of the first study (0.3 mg/kg; Gledhill, 1997a). For 21 days, six volunteers were given DDVP (98% pure; 7mg/day or 0.1 mg/kg/day for a 70 kg male) and three volunteers received corn oil in capsules (Gledhill, 1997c). Volunteers 1, 5 and 9 received placebo. Compared with the placebo group, the treated group mean erythrocyte ChE activity (% of predose level) was significantly (p<0.01) decreased on days 7 (91%), 11 (90%), 14 (86%), 16 (86%), and 18 (84%). No treatment-related clinical signs were observed.

The author of the reports established an acute NOEL of 1.0 mg/kg, the highest dose tested with 10% of erythrocyte ChE inhibition and no clinical signs. For subchronic exposure, the NOEL was 0.3 mg/kg/day since erythrocyte ChE inhibition was no more than 31% during the 21-day exposure to 0.3 mg/kg/day. No clinical signs were observed at either dose. A chronic NOEL of 0.1 mg/kg/day was extrapolated from the NOEL of 0.3 mg/kg/day in the 21-day human study (Gledhill, 1997c) and the observation that erythrocyte RBC inhibition did not progress for up to 1 year in a chronic dog study (Markiewicz, 1990).

The Medical Toxicology Branch recommended different NOELs for risk assessment based on reviews of these studies as well as those conducted in experimental animals. There were three major concerns with the current human studies: (1) the author discounted erythrocyte ChE inhibition up to 30% as treatment related, (2) only gross symptoms were reported; they did not address more subtle nervous system changes detected by standardized assays, and (3) only acute and subchronic exposures were conducted. The recommended NOELs were: 0.5 mg/kg from the human study since there was significant erythrocyte ChE inhibition at 1.0 mg/kg. The subchronic NOEL should be 0.1 mg/kg/day based clinical signs and brain ChE inhibition in the rat neurotoxicity study (Lamb, 1993b). The chronic NOEL should be 0.05 to 0.1 mg/kg/day, with 0.05 mg/kg/day based on 1-year brain ChE inhibition in dogs (Markiewicz, 1990), and 0.1 mg/kg/day suggested by the registrant based on the subchronic human study (Gledhill, 1997c).

IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

In the 1996 RCD, critical NOELs for risk assessment were derived from animal studies because dose-response relationships could not be determined from available human toxicity studies. For both acute and chronic exposures, route-specific critical NOELs were determined for the inhalation (occupational and residential) and oral (dietary) routes of exposure. The endpoints were brain ChE inhibition and clinical signs because of ChE inhibition.

Results from the recent human studies were consistent with previous human studies in that erythrocyte ChE inhibition was not accompanied by cholinergic signs and that the activity recovered to pre-exposure level upon withdrawal from DDVP exposure (Cavagna *et al.*, 1969 and 1970; Slomka and Hine, 1981; Menz *et al.*, 1974; and Rasmussen *et al.*, 1963)   To determine whether the results should be used for risk assessment, the following issues were considered:

(1)   erythrocyte ChE inhibition as a toxicity endpoint,
(2)   route-to-route extrapolation, and
(3)   time extrapolation

For the first issue, erythrocyte ChE inhibition is generally not considered an adverse effect without clinical signs since the physiological function of erythrocyte ChE is unknown. However, erythrocyte ChE is the same as the predominant form of ChE in the brain. Results from subchronic and chronic studies in laboratory animals showed that the NOELs for DDVP inhibition of erythrocyte corresponded to those for brain cholinesterase within the same study (for example, Markiewicz, 1990; Blair, 1974; Tyl, 1990; Kleeman, 1988; Thorpe *et al.*, 1971; The Hine Lab., 1962). However, the relationship was complicated by potential regional brain sensitivities to DDVP. In rats, the NOEL for brain ChE inhibition was 0.1 mg/kg/day in the cortex compared to 7.5 mg/kg/day in the brainstem, and > 15 mg/kg/day in other brain regions and erythrocyte ChE (Lamb, 1993b). A correlation between brain ChE inhibition and clinical signs could not be determined since brain ChE activity was determined at the end of the experiment while clinical signs were generally observed during the experiment. Therefore, DDVP-induced erythrocyte ChE inhibition is a valid indicator of ChE activity in the whole brain; however, it may underestimate the effect to certain regions of the brain.

The second issue is route-to-route extrapolation; that is, are the results from the oral studies appropriate for inhalation exposure? Comparisons were made between the oral and inhalation routes on pharmacokinetics, lethal concentrations, and cholinesterase inhibition activities. In the rat, pharmacokinetics data showed that excretion routes, tissue distribution, and urinary metabolites were similar following inhalation (nose only) or oral exposures to DDVP (Hutson *et al.*, 1971). However, the toxicity between the routes was different and could not be accounted for on the basis of whole body inhalation versus oral exposures (Table 1). For pupil constriction in rats, the acute oral NOEL was 0.50 mg/kg (Lamb, 1992), 16 times lower than the 8 mg/kg for the inhalation routes (Blair *et al.*, 1975). On the other hand, the oral LD50 (56-80 mg/kg; Gaines, 1960) was much higher than the inhalation LC50 of 2.4 mg/kg/day (14.8 mg/m^3 for 4 hours; Denka Chemie BV, 1982). The difference may be due to experimental and observational variations between studies. Human pharmacokinetics and toxicity studies were inadequate to make similar comparisons. Therefore, the human oral studies were not used to assess the potential effects from inhalation and dermal exposures to DDVP because of the uncertainty for route-to-route extrapolation.

Table 1. Comparison of toxicity between routes of exposure.

	rat oral	rat inhalation	human oral
acute NOEL	0.50 mg/kg (pupil constriction, gait alteration at 1.0 mg/kg; death at 80 mg/kg)	8 mg/kg (pupil constriction at 14 mg/kg)	1.0 mg/kg/day (no erythrocyte ChE inhibition, no signs)
LD50	56-80 mg/kg	2.4 mg/kg (14.8 mg/m^3)	

        The third issue was whether results from the 21-day study can be used to address chronic exposure (1 year). For DDVP, there was evidence of cumulative toxicity on erythrocyte ChE inhibition in humans (Gledhill, 1997a and c). With prolonged exposure, the subchronic NOEL (0.1 mg/kg/day) was lower than the acute NOEL of 1.0 mg/kg/day. This was likely due to the known slow turnover time (45-68 days for rats) for erythrocytes (Schalm *et al.*, 1975). From experimental animal studies, cumulative effect was also observed after oral exposure to DDVP (as discussed in the 1996 RCD **IV.A. HAZARD IDENTIFICATION**).   After oral subchronic exposure (2 weeks), the effective DDVP doses for 75% or 50% brain ChE inhibition were 3-fold higher than those for chronic exposures (Table 14 in the 1996 RCD). Because of potential cumulative toxicity, the NOEL for risk assessment should be based on chronic studies.

        Based on the above considerations, the NOEL of 0.5 mg/kg from the human study (Gledhill, 1997b) was used to select the critical NOEL for acute dietary exposure assessment. This is the same as the critical NOEL previously derived from the rat neurotoxicity study. Given the uncertainty for route-to-route and time extrapolations, the critical NOELs for other exposure scenarios remained the same as in the 1996 RCD (Table 2). In addition to hazard identification, the results of the human study were considered in the issue of interspecies extrapolation (in **IV. RISK APPRAISAL**).

B. EXPOSURE ASSESSMENT

        There was no new information on the exposure assessment.

C. RISK CHARACTERIZATION

        Based on the critical NOEL of 0.5 mg/kg, the MOEs for acute dietary exposure remained the same and ranged from 303-1027 since the NOEL was the same as that in the RCD. However, the benchmark for acceptability of health concern would be 10 instead of 100, since the critical NOEL was based on a human study. There was no change in the MOEs for chronic dietary exposure. The 1-year dog study (NOEL of 0.05 mg/kg/day) used in the RCD was more appropriate to evaluate chronic effects than those from the 21-day human study. Since these human studies were not appropriate for lifetime and non-dietary exposures, the MOEs for occupational and residential exposures, and oncogenic risks for lifetime dietary exposures remained the same.

Table 2. **The critical no-observed-effects levels (NOELs) and potency factors for risk characterization.**

Scenarios	Routes of exposure	Adjusted [a] NOEL ug/kg-day	Effects/species	References[b]
Acute				
occupational residential combined	inhalation	325	death/rabbit (2-3 days)	Thorpe *et al.,* 1971
dietary	oral	500	erythrocyte ChE inhibition/human	Gledhill, 1997b
Chronic				
occupational residential combined	inhalation	25	brain ChE inhibition, ↓ body weights/rat	Blair *et al.,* 1974
dietary	oral	50	brain ChE inhibition/dog	Markiewicz, 1990*
	Potency factors	rat mg/kg-day^{-1}		
Lifetime	oral	q_1=0.058 q_1*=0.10	mononuclear leukemia/rat	Chan, 1989*

[a] Inhalation NOELs in mg/m^3 were adjusted by converting doses to mg/kg-day units using equations in Appendix D (1996 RCD) and corrected for absorption factor (50%). The oral absorption was assumed to be 100%.

[b] * indicates study was acceptable to DPR according to FIFRA guidelines.

IV. RISK APPRAISAL

The most relevant studies for human health risk assessment are those conducted using humans. However, human studies are often not available or adequate for risk assessment. When studies from experimental animals are used, an interspecies extrapolation factor of 10 is used with the assumption that humans are 10 times more sensitive than experimental animals. With the availability of human studies, the database was reviewed for potential differences in sensitivity to DDVP toxicity. Based on data available, the comparison was limited to clinical signs and erythrocyte ChE inhibition in humans and rats from oral exposure to DDVP.

The comparison showed that the human and rat sensitivities to DDVP depended on the endpoint. After acute exposure by gavage, rats given 1.0 mg/kg DDVP showed alteration of gait (Lamb, 1992 and 1993a). At the same dose in capsules, no clinical signs were observed in humans. These results suggested that humans were less sensitive than rats.   From subchronic studies, clinical signs were noted in rats dosed with 7.5 mg/kg/day (NOEL=0.1 mg/kg/day) for 3 weeks (Lamb, 1993b) or 15 mg/kg/day (NOEL=1.5 mg/kg/day) for 6 weeks (Kleeman, 1988). Since the highest dose tested (0.3 mg/kg/day for 15 days) in humans was less than 1/10 of the lowest-observed-effect dose in rats, it was not known if clinical signs would be observed at higher doses.

On the other hand, when erythrocyte ChE inhibition data were compared, humans may be more sensitive (more than 10-fold) than rats. In rats given 4 mg/kg DDVP for 1 month, erythrocyte ChE activity was inhibited on day 24 (10%) and day 32 (10-20%) (Chan, 1989). In a 13-week study, the male rat exposed to 15 mg/kg/day showed 28% erythrocyte ChE inhibition after 3 weeks of exposure (Lamb, 1993b). The magnitude of the inhibition from these rat studies was similar to those observed in the human study at a lower dose (Glenhill, 1997a). In the 15 day study, humans exposed to 0.3 mg/kg/day showed erythrocyte ChE inhibition of 15-27% after 5 to 15 days of exposure. Therefore, a 10-fold interspecies extrapolation factor is needed to address the variable comparative sensitivity between species, when animal data were used to assess the risk of DDVP in humans.

The potential increased sensitivity to DDVP by infants and children, provision in the 1996 Food Quality Protection Act (August, 1996), was not specifically addressed in the 1996 RCD. While DDVP is not a developmental toxicant, clinical signs were observed in pups from dams exposed to 200 and 400 ppm DDVP in the drinking water during gestation and lactation (Tyl, 1990). The fetal NOEL was 80 ppm (11 mg/kg/day based on gestation dosages). Since this NOEL was much higher than the NOEL (0.05 mg/kg/day) used to assess chronic exposure, an additional uncertainty factor was not shown.

VI. TOLERANCE ASSESSMENT

Based on the NOEL of 0.5 mg/kg/day for cholinergic signs in rats, the MOEs for raw agricultural commodities, milk, eggs, and meat were greater than 100. The lowest MOE was 160 for the potential exposure of children (1-6 years) to lettuce with the residue at the tolerance.

VII. CONCLUSIONS

The recently completed human studies provided a more appropriate NOEL for acute dietary exposure only. The use of this NOEL did not change the previous conclusion that MOEs for nononcogenic effects from dietary exposure were above the benchmark considered sufficient for the protection of human health. Uncertainties in route-to-route extrapolation and time extrapolations precluded the use of the human studies for occupational and residential exposures, and chronic and lifetime dietary exposures. The MOEs remained below the benchmark for all people occupationally exposed to DDVP alone and in combination with home exposure on an acute, chronic, and lifetime basis; people exposed through residential use on an acute, chronic, and lifetime basis; and people exposed to DDVP in the diet for a lifetime.

VIII. REFERENCES

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