8-12-96

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

Chemical Name: Fonofos

PC Code: 041701

Structure

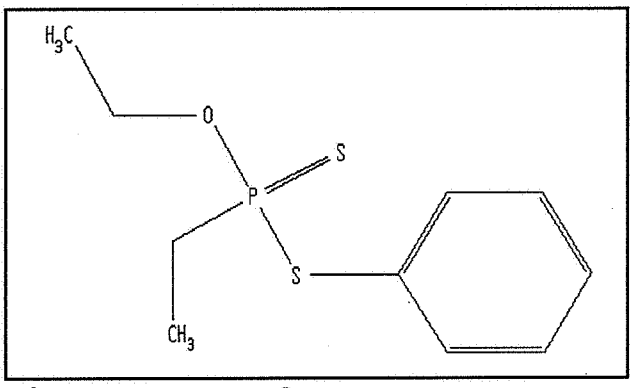

Figure 1 Fonofos

The Health Effects Division Toxicology Endpoint Selection Committee considered the available toxicology data for fonofos at a meeting held on August 6, 1996. Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

TOXICOLOGIST: _____ Date: _____
PAMELA M. HURLEY

SECTION HEAD: _____ Date: _____
ROGER GARDNER

BRANCH CHIEF: _____ Date: _____
KARL BAETCKE

1/10

DERMAL ABSORPTION DATA

No dermal absorption data are available for this chemical.

% absorbed: Based on the available toxicity data, dermal absorption is considered to be 100% until a dermal absorption study becomes available.

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ACUTE DIETARY ENDPOINT (ONE DAY)

Study Selected - Developmental Toxicity Study (rabbits) Guideline No.: 83-3b

MRID No.: 40150122

Summary: Technical fonofos (94%) was tested in a rabbit developmental toxicity study at 0, 0.2, 0.5 or 1.5 mg/kg/day. Eighteen New Zealand White rabbits per group were administered the test material by gavage on gestational days 7 through 19. A range-finding study was also conducted in which 5 rabbits/group were administered the test meterial by gavage at the following dose levels: 2.0, 4.0 or 6.0 mg/kg/day up to 10.0 mg/kg/day. The maternal NOEL for the main study is 1.5 mg/kg/day (HDT). The NOEL for developmental effects in the main study is also 1.5 mg/kg/day (HDT). The latter NOEL is borderline because there was a non-statistically significant increase in the number of resorptions/doe in the high-dose group. It was decided that this increase was not toxicologically significant because it was not statistically significant, it is within the historical control range and because the standard deviation for this measurement was so large. For the main study, the does were considered to be tested at a sufficiently high dose level because in a range-finding study maternal toxicity was observed at 2.0 mg/kg/day and above (Core Minimum). In the range-finding study, at 2.0 mg/kg/day, 1/5 rabbits died on the 5th day of dosing. At 4.0 mg/kg/day, 2/5 rabbits died on the second day of dosing and at 6.0 mg/kg/day and above 5/5 rabbits died on the second through the fourth days of dosing.

Dose and Endpoint for use in risk assessment: NOEL: 2.0 mg/kg/day based on deaths in 2 of 5 rabbits on the second day of dosing at 4.0 mg/kg/day in the developmental range-finding study.

Comments about study and/or endpoint: This dose is supported by the NOEL of 4 mg/kg/day established in an acute neurotoxicity study in the rat where clinical signs indicative of neurotoxicity (reduced foot withdrawal reflex, shaking, signs of urinary incontinence, tip toe gait and upward curvature of the spine) were observed at 6 hours post-dosing at 7 mg/kg/day (LOEL)

This risk assessment is required.

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SHORT TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 TO 7 DAYS)

DERMAL EXPOSURE:

Studies Selected - 98-day feeding study in dogs, Guideline No.: 82-1b; Chronic feeding study in dogs, Guideline No.: 83-1b; Rabbit developmental toxicity study with range-finding study, Guideline No.: 83-3b

MRID Nos.: 00090818, 43914601, 40150122

Summaries: Dyfonate (fonofos) was tested in a 98-day feeding study in beagle dogs at dose levels of 0, 8, 16, 60 or 240 ppm (0, 0.2, 0.4, 1.5 or 6.0 mg/kg/day). Two/sex/dose were tested. 0.2 mg/kg/day was only administered for 5 weeks. At 0.4 mg/kg/day, decreases in red blood cell cholinesterase activity and slight inhibition of brain cholinesterase activity were observed at 14 weeks. A convulsive seizure was observed at week 2 in one animal (none at higher dose levels). At 1.5 mg/kg/day, decreases in plasma and red blood cell cholinesterase activity were observed at 14 weeks. Slight emesis and soft stools were also observed during the first month and increases in lacrimal and salivary secretions were observed "throughout the study". At 6.0 mg/kg/day, 2 dogs had slight tremors and anxiety throughout the study. Again, slight emesis and soft stools were observed during the first month and increases in lacrimal and salivary secretions were observed "throughout the study". Decreases in activity of all 3 cholinesterase parameters were observed at 14 weeks. The systemic NOEL was 0.2 mg/kg/day based on the convulsive seizures of one animal at week 2. The systemic LEL was 0.4 mg/kg/day. The NOEL for cholinesterase activity was less than 0.4 mg/kg/day (lowest dose tested for the full 14 weeks) (Supplementary).

In a chronic toxicity study fonofos (94.6% a.i.) was administered to groups of 4 beagle dogs/sex/dose by capsule at dose levels of 0, 0.2, 0.4 or 1.75 mg/kg/day in corn oil for a period of at least one year. At 0.2 mg/kg/day, minimal sporadic plasma cholinesterase inhibition was observed in both sexes (7-13%; 20% only once at 52 weeks in females). At 1.0 mg/kg/day, there were increases in alkaline phosphatase levels (130-194% of control values) and inhibition of erythrocyte (51% in males, 53% in females) and plasma cholinesterase (50% in both sexes) activities. At 1.75 mg/kg/day, there were clinical signs of toxicity in one animal, decreases in serum albumin and total protein levels, increases in alkaline phosphatase levels (up to 217%), inhibition of erythrocyte (62% in males, 63% in females), plasma (57% in males, 58% in females) and possibly brain (20% in females) cholinesterase activities and increases in absolute liver weights in males (18.5%). One female dosed with 2.0 mg/kg/day for 3 days developed clinical signs and intussusception of the terminal ileum, possibly due to uncontrolled peristaltic movement following substantial depression of cholinesterase activity. The NOEL is 0.2 mg/kg/day. The NOEL is considered to be a borderline NOEL/LOEL because there was minimal plasma cholinesterase inhibition at 0.2 mg/kg/day which was generally weak and was not consistent. The LOEL, 1.0 mg/kg/day is based on plasma and erythrocyte cholinesterase inhibition and increases in alkaline phosphatase levels at 1.0 mg/kg/day and above, and clinical signs of toxicity, decreases in selected blood chemistry values, increases in liver weights and histologic changes in the ileum at 1.75 mg/kg/day (Acceptable).

See summary of rabbit developmental study in previous section.

Dose and Endpoint for use in risk assessment: The NOEL selected was 1.5 mg/kg/day from the 98-day dog study, a dose above which effects were observed within the first few days of each of the three co-critical studies.

Comments about study and/or endpoint: At 2.0 mg/kg/day in the rabbit study, death was observed in one animal by the 5th dosing day. At 1.75 and 2.0 mg/kg/day in the chronic dog study, clinical signs of toxicity were observed in several dogs on day 3. The effects seen at 1.5 mg/kg/day and at 0.4 mg/kg/day, the next lower dose level in the 98-day dog study were observed later in the study and were not considered relevant to short term exposure. Since an oral study was used for this exposure scenerio a dermal absorption factor of 100% should be used for this risk assessment.

This risk assessment is required.

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INHALATION EXPOSURE:

Study Selected - Guideline No.: No long term inhalation studies are available. Based on the LC_{50} of 50 μg/L in males and 17.9 μg/L in females, Fonofos is placed in Toxicity Category I. Therefore, the risk assessment should be inclusive of the inhalation (100%) plus the dermal (100%) exposures.

INTERMEDIATE TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 WEEK TO SEVERAL MONTHS)

DERMAL EXPOSURE:

Study Selected - Guideline No.: 90-day mammalian neurotoxicity study - 82-7

MRID Nos.: 42792601 and 43030101

Summary:: Fonofos (Dyfonate®) was tested in a subchronic mammalian neurotoxicity feeding study in Alpk:APfSD rats at the following dose levels for 90 days: 0, 15, 50 or 125/150 ppm (0, 0.75, 2.5, or 6.25/7.5 mg/kg/day). The highest dose level was changed from 125 ppm to 150 ppm at week 5. Twelve rats/sex were tested at each dose level. The following parameters were observed and measured: clinical signs of toxicity, body weights, food consumption, functional observational battery, motor activity, brain measurements, cholinesterase activity and neuropathology. Six animals/sex in each group were designated for terminal neuropathology, although only the high dose group and controls were ultimately examined. At 15 ppm, statistically significant decreases in erythrocyte cholinesterase activity (both sexes) and in plasma cholinesterase activity (females) were observed. At 50 ppm and above, statistically significant decreases in cholinesterase activity were observed in both sexes for all 3 parameters. At 125/150 ppm, treatment related clinical signs were observed in females. These included upward curvature of the spine, tiptoe gait, signs of urinary incontinence, pinched in sides, reduced splay reflex, splayed gait, eye bulging and shaking. In addition to these, decreases in the motor activity observations were noted for females. There were no microscopic indications of neurotoxicity. The NOEL is 50 ppm and the LEL is 125/150 ppm based on clinical signs of toxicity and on decreases in motor activity. The NOEL for cholinesterase inhibition is 15 ppm and the LEL is 50 ppm based on decreases in cholinesterase activity in all 3 parameters at 50 ppm (Core Guideline).

Dose and Endpoint for use in risk assessment: NOEL: 0.75 mg/kg/day based on decreases in RBC, plasma and brain cholinesterase activities in both sexes (starting at week 4 for plasma and RBC activities). LOEL: 2.5 mg/kg/day.

Comments about study and/or endpoint: Since an oral study was used for this exposure scenario, a dermal absorption factor of 100% should be used for this risk assessment.

This risk assessment is required.

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INHALATION EXPOSURE (INTERMEDIATE):

Study Selected - Guideline No.: See inhalation discussion under the short-term exposure section.

CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

DERMAL EXPOSURE:

Study Selected - Guideline No.: Chronic feeding study in the dog (83-1b)

MRID No.: 43914601

Summary: (Enter Standard Executive Summary or equivalent): See summary provided in the short term exposure section.

Dose and Endpoint for use in risk assessment: NOEL: 0.2 mg/kg/day based on decreases in erythrocyte and plasma cholinesterase activities and increases in alkaline phosphatase levels at 1.0 mg/kg/day (LOEL).

Comments about study and/or endpoint: This study was used to establish the RfD. Since an oral study was used for this exposure scenario, a dermal absorption factor of 100% should be used for this risk assessment.

This risk assessment is required.

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INHALATION EXPOSURE:

Study Selected - Guideline No.: See inhalation discussion under the short-term exposure section.

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CANCER CLASSIFICATION AND BASIS:

Q_1* = N/A. This chemical was classified in Group E for carcinogenicity: no evidence of carcinogenic activity in rats or mice under the conditions of the studies.

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RfD AND BASIS: 0.002 mg/kg/day

NOEL for critical study: 0.2 mg/kg/day with uncertainty factor of 100.

Study Type - Guideline No.: Chronic feeding study in the dog (83-1b)

MRID: 43914601

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ACUTE TOXICITY ENDPOINTS:

Acute Toxicity Values for Fonofos				
Guideline No.	**Study Type**	**MRID No.**	**Study**	**Category**
81-1	Acute oral	00078777	LD_{50} males: 24.5 mg/kg LD_{50} females: 10.8 mg/kg	I
81-2	Acute dermal	00078777	LD_{50} both sexes: 159 mg/kg	I
81-3	Acute inhalation	41935901	LC_{50} males: 51.0 μg/l LC_{50} females: 17.9 μg/l	I
81-4	Primary eye irritation	00078777	Mean score of 0.33 at 24 hours: non-irritating.	III
81-5	Primary dermal irritation	00078777	No irritation for 4/6 animals at 72 hours. Two animals died at 24 hours.	IV
81-6	Dermal sensitization	42842601	A weak to mild sensitizer under conditions of study.	N/A
81-7	Acute delayed neurotoxicity	43161301	No clinical evidence of acute delayed neurotoxicity. Overall, fonofos induced an equivocal response.	N/A
81-8	Acute mammalian neurotoxicity	42777801 & 43030101	NOEL: 4 mg/kg; LOEL: 7 mg/kg based on clinical signs of toxicity.	N/A

Acute oral toxicity studies in male and female rats indicated that oral exposure to fonofos induces clinical signs of toxicity that are typical of cholinesterase inhibitors. In males at the LD_{50} level, these signs included depression, tremors, copious salivation, diarrhea, bulging eyes, lacrimation, labored breathing and wet yellow stains around the ano-genital region. By day 6, these symptoms had disappeared. Any deaths occurred within 6 hours after dosing. In females at the LD_{50} level, depression, tremors, shallow breathing, blood-like stains around the facial area and yellow stains around the ano-genital region were observed. These signs disappeared by day 4. Deaths occurred within 22 hours.

An acute dermal toxicity study in rabbits indicated that dermal exposure to fonofos induces similar clinical signs of toxicity. At 200 mg/kg, depression, tremors, salivation, diarrhea, rapid breathing and constricted pupils were observed in both sexes. These symptoms disappeared by day 4. Any deaths occurred within 5 hours. Necropsy of the animals which died showed red and irritated stomachs, darkened lungs and pale livers. Although only 3 or 4 rabbits/sex were tested/dose level, the study was considered acceptable because the results were consistent with the other acute toxicity studies.

An acute inhalation toxicity study was conducted on rats using a 4 hour exposure. The median lethal concentration was based on the atmospheric concentrations achieved in the study. Clinical signs of toxicity and cholinesterase inhibition were evident and were consistent with combination of neurological and irritancy effects which are typical of those seen following exposure to organophosphorus compounds.

In the primary dermal irritation study with rabbits, 0.05 ml was given as a dose instead of the required dose of 0.5 ml/site (0.2 ml/animal or 100 mg/kg) because in a previous study using 0.5 ml of 93% technical fonofos with Aliquot 335, all the animals had died. One hundred mg/kg had killed 2/6 animals in the acute dermal study.

In the primary eye irritation study, 0.01 ml was tested because in other eye irritation studies with technical dyfonate, all the animals died with a dose of 0.1 ml with no irritation. No rabbits died in this study. At 24 hours, 1/6 rabbits with unwashed eyes had a score of 2. This score was 0 by 48 hours. No other rabbits, either unwashed (6 animals) or washed (3 animals) had any reaction at any time. The mean score at 24 hours was 0.33. This corresponds to a rating of non-irritating. However, since one rabbit had an effect at 24 hours, this places the chemical in Toxicity Category III.

In the dermal sensitization study conducted with guinea pigs, a version of the maximisation test of Magnusson and Kligman was used. Formaldehyde was used as the positive control and provided an appropriate positive response.

A dose level of 143 mg/kg was selected for the acute delayed neurotoxicity study based on the results of a range finding study and an acute LD_{50} study. Atropine was injected both prior to and after dosing instead of just prior to dosing. The fonofos treated birds displayed clinical signs of toxicity (unsteadiness, inability to stand and subdued behavior) which disappeared by day 6 in surviving birds. There was no clinical evidence of delayed neurotoxicity (ataxia) in the treated birds and the levels of neurotoxic esterase (NTE) for these birds were similar to vehicle controls. The positive control birds gave a weak positive response for delayed ataxia, but displayed a strong reduction in NTE. There was a 51% reduction in acetyl cholinesterase levels in the brain for the fonofos treated birds when compared to vehicle controls. Trace axonal degeneration was observed in the spinal cord and peripheral nerves of 5/6 of the vehicle controls. In the positive control birds, 4/6 birds showed minimal axonal degeneration in the spinal cord and 1/6 in the proximal sciatic nerve. In addition, trace axonal degeneration was observed in the cerebellum of 3/6 birds. In the fonofos treated birds, trace axonal degeneration was observed in the spinal cord and the peripheral nerves of 6 birds and in the cerebellum of 1 bird. In one bird, significant axonal degeneration (moderate or marked) was observed in the distal sciatic and tibial nerves on the right side only. In light of the facts that there was no clinical evidence of acute delayed neurotoxicity, there was no evidence of a decrease in NTE activity in animals treated with fonofos in this study, the positive controls displayed an unusually weak response and there was no evidence of delayed neurotoxicity in the 90-day study, this finding is considered to be an equivocal response. Therefore, fonofos is considered to have induced an equivocal response in the acute delayed neurotoxicity study.

In the acute mammalian neurotoxicity study, 0, 2, 4 or 7 mg/kg were tested. At 7 mg/kg, 1/10 females displayed reduced foot withdrawal reflex, shaking, signs of urinary

incontinence, tip toe gait and upward curvature of the spine 6 hours after dosing. Recovery in this animal was observed by 24 hours. The NOEL is 4 mg/kg and the LOEL is 7 mg/kg based on clinical signs of toxicity.