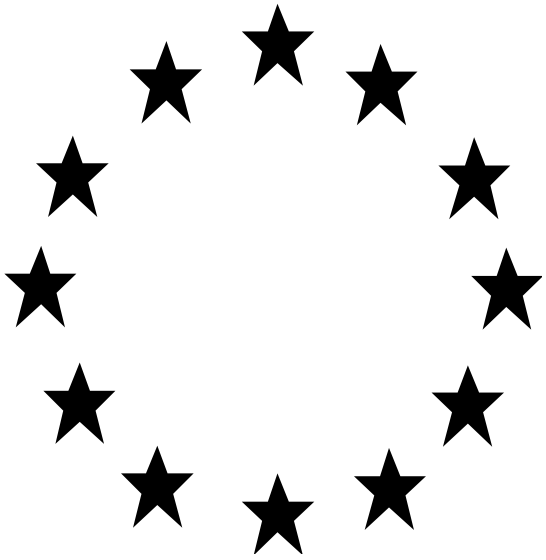

Draft Assessment Report (DAR)

- public version -

Initial risk assessment provided by the rapporteur Member State Sweden for the existing active substance

TOLCLOFOS-METHYL

of the second stage of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC

Volume 3, Annex B, B.6, part 3

January 2005

B.6.10.2 Acute studies

Tolclofos-methyl has low acute toxicity when administered orally, dermally and via inhalation to rats. It is not a skin or eye irritant. It is not a skin sensitizer by Buehler test, but a skin sensitizer by Maximization test and should be labelled with the risk phrase **"May cause sensitisation by skin contact" R43**.

After oral administration, toxic symptoms in rats and mice were decrease of spontaneous motor activity, irregular respiration, dyspnea, piloerection, incontinence of urine and ataxia of hind limb or whole body 3-4 hours after administration. The minimum toxic dose level was 3750 mg/kg bw and 1500 mg/kg bw in rats and mice, respectively. At gross necropsy, no visible lesions were observed.
Emesis and soft stools or diarrhea was observed in many of the dogs.
After inhalation, signs consistent with exposure to high concentration of a mildly irritant dust were noted, including closing or partial closing of the eyes, abnormal body position and abnormal breathing. Abnormal respiratory pattern was observed immediately after exposure.
Tolclofos-methyl did not produce any irritant reactions on the skin nor in the eyes.

B.6.10.2-1 Summary and conclusions on acute toxicity studies

Study	Dose levels	Results
Segawa, 1978 Acute oral toxicity study in rats and mice.	Rats: 1000, 2500, 3750 or 5000 mg/kg bw Mice: 1000, 1500, 2000, 3000 or 4000 mg/kg bw	Rats: LD_{50} around 5000 mg/kg bw Mice: LD_{50} 3500 mg/kg (male), 3600 mg/kg (female)
Kynoch, 1985a Acute oral toxicity study in rats	500*, 1000* or 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw
Pence 1978 Acute oral toxicity study in dogs	100, 215, 464 or 1000 mg/kg bw	LD_{50} > 1000 mg/kg bw
Parcell et al., 1994 Acute oral toxicity study in rats (Cholinesterase estimations)	2, 200 or 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw No effect on cholinesterase levels
Segawa 1978 Acute dermal LD_{50} in rats and mice	Rats: 1000, 2500 or 5000 mg/kg bw Mice: 0, 1000, 2500 or 5000 mg/kg bw	LD_{50} > 5000 mg/kg LD_{50} > 5000 mg/kg
Kynoch et al., 1985b Acute dermal LD_{50} in rabbits	2000 mg/kg bw	LD_{50} > 2000 mg/kg
Hardy et al., 1986 Acute inhalation LC_{50} (4 hours) in rats	0, 1.35 or 3.32 mg/l	LC_{50} > 3.32 mg/l
Matsubara et al., 1978 Acute skin irritation in rabbits	500 mg	Non irritant
Ligget et al., 1985a Acute skin irritation in rabbits	500 mg	Non irritant
Matsubara et al., 1978 Acute eye irritation in rabbits	50 mg	Non irritant
Ligget et al., 1985a Acute eye irritation in rabbits	75 mg	Non irritant
Seaber 1985 Skin sensitization in guinea pigs - Buehler test	0.5 ml of 50% (induction), 0.5 mL of 50% (challenge)	Non sensitizing
Nakamura 2001 Skin sensitization in guinea pigs - Maximization test	0.1 mL of 5% (intradermal induction), 0.4 mL of 25% (demal induction), 0.2 mL of 10% (challenge)	Sensitizing **R43**

** used only in preliminary study*

B.6.10.3 Short-term toxicity

Following repeated oral administration of high doses of tolclofos-methyl, no evidence for cumulative toxicity was seen in rats, mice or dog.

In the three species, reduced body weight development and reduced food intake were noted at the highest dose levels, except for food intake in mice.

Reduced cholinesterase levels were seen in several studies and in all species.

In rats, increased levels of cholesterol, total proteins and inorganic phosphorus were noted, as well as decreased cholinesterase activity (mainly in brain and plasma). Target organs were kidneys and liver, with increased weights. Hypertrophy of the hepatocytes was noted in rats after 4-week or 90-day treatment. It was not observed in the 6-month study.

Mice were the less sensitive species with only inhibition of plasma, erythrocyte and/or brain cholinesterase activities, without any other relevant modifications in haematological or clinical chemistry parameters, or in organ weights.

In dogs, haematological changes consisted of decreased erythrocyte count, hematocrit and haemoglobin values. Clinical chemistry showed elevated alkaline phosphatase values. Decreased albumin values were also noted. Liver was the target organ with increased weight and hypertrophy of the hepatocytes. Changes in the weight of kidneys, prostate and pancreas were also noted.

Dermal irritation was evident in many rabbits, in the form of very slight erythema. Significantly increased mean eosinophil values were noted in the males treated at 1000 mg/kg bw/day. Plasma cholinesterase levels were reduced. Increased weight of kidneys was seen in the females. Histopathology evaluation only revealed hyperkeratosis, acanthosis, and subepidermal pleocellular infiltration in most animals of all treated groups.

Table B.6.10.3-1 Summary and conclusions on short-term toxicity studies

Study	Dose levels	NOEL/NOAEL	Targets/main effects
Colley et al., 1982 Oral 4-week toxicity study in rats	0, 200, 1000, 5000, 20000 ppm M/F: 0, 16, 79, 414, 1635 0,18, 88, 452, 1830 mg/kg bw/day	**NOAEL** 5000 ppm (414 mg/kg bw/day) LOEL 200 ppm (16 mg/kg bw/day) NOEL < 200 ppm	**↓Body weight gain** **↑Liver weights** **Hepatocyte enlargement** ↓Cholinesterase (dose response for brain) levels ↑Cholesterol, total protein, albumin, inorganic phosphorus ↓Food consumption Changes in kidney weight
Kimura 1990 Oral 90-day toxicity study in rats	0, 100, 1000, 10000 ppm M/F: 0, 6.46, 66.1, 653/ 0, 7.13, 71.0, 696 mg/kg bw/day	**NOAEL** 1000 ppm (66.1 mg/kg bw/day) NOEL 100 ppm (6.46 mg/kg bw/day)	**↑Liver weight** **Hypertrophy of hepatocytes** ↓Body weight gain ↓Cholinesterase levels ↓Food consumption Changes of haematological and chlinical chemistry parameters
Hiromori et al., 1978; Takatsuka, 1985a Oral 6-month toxicity study in rats	0, 300, 1000, 3000, 10000 ppm M/F: 0, 16, 51, 164, 540/ 0, 18, 65, 184, 623 mg/kg bw/day	**NOAEL** 3000 ppm (164 mg/kg bw/day) NOEL 300 ppm (16 mg/kg bw/day)	**↓Body weight, body weight gain** **↑Kidney, liver and testes weights** ↓Haemoglobin concentration ↓Plasma cholinesterase, uric acid
Pence et al., 1979b; Cox, 1987 Oral 6-month toxicity study in dogs	0, 200, 600, 2000 ppm M/F: 0, 6.6, 24, 70/ 0, 6.0, 21, 63 mg/kg bw/day	**NOAEL** 600 ppm (21 mg/kg bw/day) NOEL 600 ppm (21 mg/kg bw/day)	**↓Body weight gain** **↑Alkaline phosphatase** **↑Liver weights** ↓Hematocrit, erythrocyte and haemoglobin values ↓Plasma cholinesterase

Study	Dose levels	NOEL/NOAEL	Targets/main effects
Cox, 1988, 1993; Moore, 1993 Oral 12-month toxicity study in dogs	0, 80, 400, 2000 ppm M/F: 0, 2.2, 11.4, 59/ 0, 2.6, 11.2, 62 mg/kg bw/day	**NOAEL** 400 ppm (11 mg/kg bw/day) NOEL 80 ppm (2.2 mg/kg bw/day)	**↑Liver and pancreas weight** **↓Prostate weight** **↑Hepatocytic hypertrophy** **↑Alkaline phophatase** Based on non-adverse effects on hepatocytic piment at 400 ppm and changes at 2000 ppm: ↓Erythrocyte count, hematocrit, and haemoglobin values F: ↓Albumin, total protein ↑Reducing substances in urine
Suzuki et al., 1978 Oral 9-month toxicity study in mice	0, 10, 30, 100, 3000 ppm M/F: 0, 1.2, 3.8, 12.2, 513/ 0, 1.4, 4.1, 13.8, 564 mg/kg bw/day	**NOAEL** 100 ppm (12.2 mg/kg bw/day) LOEL 10 ppm (1.42 mg/kg bw/day) NOEL < 10 ppm	**↓Body weight, body weight gain** **↓Cholinesterase levels**
Gargus et al., 1986 Percutaneous 21-day in rabbits	0, 30, 300, 1000 mg/kg bw/day	**NOAEL** (systemic) >1000 mg/kg bw/day NOEL (systemic) 30 mg/kg bw/day NOEL (local) <30 mg/kg bw/day	 ↓Cholinesterase levels ↑Kidney weights ↑Eosinophil values ↑Dermal irritation

B.6.10.4 Genotoxicity

The mutagenic potential of tolclofos-methyl was studied *in vitro* in bacteria and mammalian cells and *in vivo* in test systems in somatic cells and in germ cells. The test systems assayed did not show evidence of tolclofos-methyl genotoxicity. Overall, the studies indicate that tolclofos-methyl does not possess any concern for genotoxicity.

Table B.6.10.4-1 Summary and conclusions on genotoxicity testing

Study	Dose levels	Result
Moriya et al., 1981 Mutagenicity assay in *Salmonella typhimurium & Escherichia coli*	0, 10, 50, 100, 500, 1000, 5000 µg/plate, +/- S9 mix	Negative
Suzuki et al., 1978 Mutagenicity assay in *Salmonella typhimurium*	0, 10, 100, 500, 1000, 2000 µg/plate, +/- S9 mix	Negative
Moriya et al., 1981 Rec-assay in *Bacillus subtilis* H17 & M45	0, 20, 50, 100, 200, 500, 1000, 2000, 5000 µg/disk	Negative
Suzuki et al., 1978 Rec-assay in *Bacillus subtilis* H17 & M45	0, 1, 10, 100, 1000 µg/disk	Negative
Suzuki et al., 1978 Host-mediated assay, male ICR mouse injected with *Salmonella typhimurium* G46	0, 870, 1750 mg/kg	Negative
Monaco et al., 1981 Gene mutation assay in Chinese hamster lung cells (V79	$5x10^{-6}$, $5x10^{-7}$, $5x10^{-8}$, $5x10^{-9}$ M, +/- S9 mix	Negative
Kogiso et al., 1990 *In vitro* chromosomal aberration test in Chinese hamster ovary cells (CHO-K1)	0, 37.5, 75, 150 µg/ml (+S9, 2+16 and 2+22 h) 0, 10, 20, 40 µg/ml (-S9, 18 and 24 h)	Negative
Monaco et al. 1981 *In vitro* unscheduled DNA synthesis test in human cervical carcinoma cells (HeLa)	$1x10^{-6}$, $1x10^{-7}$, $1x10^{-8}$, 10^{-9} M, +/- S9 mix	Negative
Hara et al., 1990 *In vitro* unscheduled DNA synthesis test in rat primary hepatocytes	0, 0.3, 1, 3, 10, 20, 40 µg/ml (18 h)	Negative
Suzuki et al., 1981 *In vivo* chromosomal aberration test of S-3349 on bone marrow cells of mice	0, 1000, 2000, 4000 mg/kg (6 and 24 h) 0, 500, 1000 mg/kg (48 h)	Negative
Brusick et al., 1981 *In vivo* study in germ cells: dominant lethal assay, male CD(SD)BR Sprague-Dawley rats	0, 62.5, 208.3, 625 mg/kg daily for 5 days	Negative

B.6.10.5 Long-term toxicity and carcinogenicity

Tolclofos-methyl did not exhibit evidence of cumulative toxicity in chronic toxicity studies in rats or mice. Some variations in organ weights were noted in the mouse (increased weights of kidneys, pituitary, and decrease in thymus weight), in the high dose group, but no change was detected in gross pathological findings at necropsy and histopathological examination. In mice, decrease in cholinesterase activity mainly in the serum was seen in the two high dose groups. Changes in the weight of pituitary and thymus was seen in females. There was no effect on general symptoms, time and number of occurrence of external masses and mortality.

In the rat, no distinct compound-related organ or tissue changes were observed in any of the animals. At terminal sacrifice as well as in the animals that died or were sacrificed in extremis during the study, the incidence of interstitial cell tumors was comparable between the compound-treated and control males. Neoplasms, spontaneous disease lesions and incidental findings were consistent with lesions routinely observed in rats of this

age and strain. No treatment-related effects were shown on the cholinesterase activity in the 104-week study in rat.

Tolclofos-methyl demonstrated no carcinogenic potential in long-term tests in the rat and mouse. The carcinogenicity data on tolclofos-methyl suggests that it does not present a concern for oncogenicity.

Table 6.10.5-1 Summary of long-term toxicity and carcinogenicity

Study	Dose levels	NOEL/NOAEL	Target/main effects
Pence et al., 1982 Chronic toxicity study (2 year) in rats, oral (diet)	0, 100, 300, 1000 ppm (4.2, 12, 42 mg/kg bw/day (males), and 4.8, 15, 49 mg/kg bw/day (females))	**NOAEL** ≥1000 ppm (42 mg/kg bw/day) NOEL ≥1000 ppm (42mg/kg bw/day)	**Not carcinogenic**
Pence et al., 1985a Chronic toxicity study (2 years) in rats, oral (diet)	0, 100, 300, 1000 ppm (4.1, 12, 42 mg/kg bw/day (males), and 4.8, 15, 49 mg/kg bw/day (females))	**NOAEL** ≥1000 ppm (42mg/kg bw/day) NOEL ≥1000 ppm (42mg/kg bw/day)	**Not carcinogenic**
Satoh et al., 1983 Chronic toxicity study (2 years) in mice, oral (diet)	0, 10, 50, 250, 1000 ppm (1.3, 6.4, 32.2, 134 mg/kg bw/day (males) and 1.3, 6.9, 34.1, 137 mg/kg bw/day (females))	**NOAEL** 250 ppm (32.2 mg/kg bw/day) NOEL 50 ppm (6.4 mg/kg bw/day)	**↓ Cholinesterase levels** ↑ Glucose ↑Pituitary weight ↓Thymus weight **Not carcinogenic**

B.6.10.6 Reproductive toxicity

A three-generation rat reproduction study conducted with tolclofos-methyl did not reveal evidence of reproduction toxicity.

During the 15-week growth periods, parental body weights, growth rates, and total food consumption were comparable between treated and control groups. Mean maternal body weights and body weight changes during gestation and lactation were comparable among groups of each generation. Growth rates of the high-dose P2 males, and the mid- and high-dose P3 males were similar to the respective controls. Increases in mean ovary weights were noted in the high-dose P3 non-pregnant females, but no abnormal histomorphologic alterations were found in the ovaries and no alterations were noted in the remaining data.

Pregnancy rates, fertility rates and parturition indices were generally comparable among groups of each generation.

There were no differences in any of the offspring viability and survival data that were attributable to treatment. Gross pathology findings for the offspring of all generations were considered incidental in nature and showed no relation to compound administration. Increased ovary weights were noted for the F1b pups at all three treatment levels. However, this was not observed for the F2b or F3b pups. Microscopic evaluation did not reveal any compound-related histomorphologic alterations in the tissues examined.

Since the results of the reproduction study provide satisfactory information and show the absence of effects on reproduction, supplementary studies are not considered to be necessary for better interpretation.

There were no dominant lethal effects induced by tolclofos-methyl.

Teratogenicity studies in rats and rabbits indicated no embryo-toxic or teratogenic effects.

In rats, the mean body weight gain and food consumption were reduced at 1000 mg/kg bw/day. Together these data indicate slight maternal toxicity at 1000 mg/kg bw/day. The number of foetuses with the 5th and/or 6th sternebrae unossified was significantly greater at 1000 mg/kg bw/day than in the control group. However, the unossification of the 5th sternebae was considered to be a developmental variation and in the variation of the 6th sternebrae there was no dose-response. Neither the type nor frequency of malformations indicated an embryo-toxic or teratogenic response. The lower implantation efficiency observed in the 50 mg/kg bw/day group was not reproduced in the second study and is therefore considered to be incidental.

In rabbits, the body weight gains were suppressed in the 1000 mg/kg bw/day group or above, food consumption was decreased and there was a slight decrease in some organ weights (kidney, spleen), showing maternal toxic effect. In addition, one dam died and three abortions occurred. Food consumption was markedly decreased in the dams in which the abortions occurred, and this was a probable cause of the abortions. Skeletal variations included eight lumbar vertebrae and 13th rib or asymmetry of sternebrae, but the incidences of these variations were not significantly increased and there were no dose-response. Neither the type nor frequency of malformations indicated an embryo-toxic or teratogenic response. There were no effects on the degree of ossification.

Table B.6.10.6-1 Summary on reproductive toxicity

Study	Dose levels	NOEL/NOAEL	Targets/main effects
Pence et al., 1985b 3 generation reproduction study in rats, oral	0, 100, 300, 1000 ppm males/females: 6.9-7.9, 20.5-23.8, 70.6-79.6 / 8.9-9.2, 26.2-28.4, 90.5-98.5 mg/kg bw/day	**Parental NOAEL/NOEL** ≥1000 ppm (134-198 mg/kg bw/day). Pup NOEL 1000 ppm Reproduction NOEL 1000 ppm	
Pence et al., 1979 Teratology study in rats, oral	0, 5, 15, 50 mg/kg bw/day	**Maternal and developmental NOAEL** ≥50 mg/kg bw/day NOEL 15 mg/kg bw/day	↓ Implamantation efficiency
Morseth et al., 1987 Teratology study in rats, oral	0, 100, 300, 1000 mg/kg bw/day	**Maternal NOAEL** ≥1000 mg/kg bw/day NOEL 300 mg/kg bw/day **Developmental NOAEL** ≥1000 mg/kg bw/day NOEL 300 mg/kg bw/day Not teratogenic	↓ Body weight gain Delayed ossification Not teratogenic

Study	Dose levels	NOEL/NOAEL	Targets/main effects
Kashima et al., 1991 Teratology study in rabbits, oral	0, 300, 1000, 3000 mg/kg bw/day	**Maternal NOAEL** 300 mg/kg bw/day Maternal NOEL 300 mg/kg bw/day Developmental NOAEL ≥3000 mg/kg bw/day	**One dam died** **Three abortions occurred** **↓Body weight gain** **↓Food consumption** ↓ Body weight ↓Kidney weight ↓Spleen weight Not teratogenic
Brusick et al., 1981 Dominant lethal assay in rats, oral	0, 65.5, 208.3, 625 mg/kg bw/day (5 days)		Negative

B.6.10.7 Delayed neurotoxicity

Tolclofos-methyl showed no acute delayed neurotoxicity in a study with leghorn hens. The NOEL was determined to be 8000 mg/kg bw/day (highest technically possible dosage), based on the absence of delayed neurotoxic signs and no histopathological changes such as axonal degeneration or demyelination.

Table B.6.10.7-1 Summary on delayed neurotoxicity

Study	Dose levels	NOEL/NOAEL	Targets/main effects
Okuno, Y. et al 1982. Acute delayed neurotoxicity, oral, hen	0 or 8000 mg/kg	**NOEL** ≥8000 mg/kg	↓Transient decrease of plasma cholinesterase levels ↓ food consumption

B.6.10.8 Acceptable daily intake (ADI)

The data of the following repeated exposure dietary study could serve as a basis for setting ADI.

Study	Dose levels	NOEL/NOAEL	Target/main effects
Satoh et al., 1983 Chronic toxicity study (2 years) in mice, oral (diet)	0, 10, 50, 250, 1000 ppm (1.3, 6.4, 32.2, 134 mg/kg bw/day (males) and 1.3, 6.9, 34.1, 137 mg/kg bw/day (females))	**NOAEL** 250 ppm (32.2 mg/kg bw/day) NOEL 50 ppm (6.4 mg/kg bw/day)	**↓Cholinesterase levels** ↑ Glucose ↑Pituitary weight ↓Thymus weight **Not carcinogenic**

The proposed acceptable daily intake (ADI) is to be established on the basis of the highest dose not causing harmful effects in the most sensitive species. In the 2 year toxicity study in mice a NOEL of 6.4 mg/kg bw/day was obtained and found suitable for a calculation of an ADI .

It is appropriate to apply an uncertainty factor of 100 to the NOEL of 6.4 mg/kg bw/day, and thus derive an ADI for tolclofos-methyl of 0.064 mg/kg bw/day.

B.6.10.9 Acceptable operator exposure level (AOEL).

The data of the following repeated exposure toxicity studies could serve as a basis for setting AOEL.

Table B.6.10.3-1 Summary of repeated toxicity studies suitable for setting AOEL

Study	Dose levels	NOEL/NOAEL	Targets/main effects
Colley et al., 1982 Oral 4-week toxicity study in rats	0, 200, 1000, 5000, 20000 ppm M/F: 0, 16, 79, 414, 1635 0,18, 88, 452, 1830 mg/kg bw/day	**NOAEL** 5000 ppm (414 mg/kg bw/day)	**↓Body weight gain** **↑Liver weights** **Hepatocyte enlargement**
Kimura 1990 Oral 90-day toxicity study in rats	0, 100, 1000, 10000 ppm M/F: 0, 6.46, 66, 653/ 0, 7.13, 71.0, 696 mg/kg bw/day	**NOAEL** 1000 ppm (66.1 mg/kg bw/day)	**↑Liver weight** **Hypertrophy of hepatocytes**
Hiromori et al., 1978; Takatsuka, 1985a Oral 6-month toxicity study in rats	0, 300, 1000, 3000, 10000 ppm M/F: 0, 16, 51, 164, 540/ 0, 18, 65, 184, 623 mg/kg bw/day	**NOAEL** 3000 ppm (180 mg/kg bw/day)	**↓Body weight, body weight gain** **↑Kidney, liver and testes weights**
Pence et al., 1979b; Cox, 1987 Oral 6-month toxicity study in dogs	0, 200, 600, 2000 ppm M/F: 0, 6.6, 24, 70/ 0, 6.0, 21, 63 mg/kg bw/day	**NOAEL** 600 ppm (21 mg/kg bw/day)	**↓Body weight gain** **↑Alkaline phosphatase** **↑Liver weights**
Cox, 1988, 1993; Moore, 1993 Oral 12-month toxicity study in dogs	0, 80, 400, 2000 ppm M/F: 0, 2.2, 11.4, 59/ 0, 2.6, 11.2, 62 mg/kg bw/day	**NOAEL** 400 ppm (11 mg/kg bw/day)	**↑Liver and pancreas weight** **↓Prostate weight** **↑Hepatocytic hypertrophy** **↑Alkaline phophatase**
Pence et al., 1985b 3 generation reproduction study in rats, oral	0, 100, 300, 1000 ppm males/females: 6.9-7.9, 20.5-23.8, 70.6-79.6 / 8.9-9.2, 26.2-28.4, 90.5-98.5 mg/kg bw/day	**Parental NOAEL/NOEL** ≥1000 ppm (70.6-98.5 mg/kg bw/day).	
Pence et al., 1979 Teratology study in rats, oral	0, 5, 15, 50 mg/kg bw/day	**Maternal and developmental NOAEL** ≥50 mg/kg bw/day	
Morseth et al., 1987 Teratology study in rats, oral	0, 100, 300, 1000 mg/kg bw/day	**Maternal NOAEL** ≥1000 mg/kg bw/day **Developmental NOAEL** ≥1000 mg/kg bw/day	
Kashima et al., 1991 Teratology study in rabbits, oral	0, 300, 1000, 3000 mg/kg bw/day	**Maternal NOAEL** 300 mg/kg bw/day **Developmental NOAEL** ≥3000 mg/kg bw/day	**One dam died** **Three abortions occurred** **↓Body weight gain** **↓Food consumption** Not teratogenic

The proposed acceptable operator exposure level (AOEL) is to be established on the basis of a NOAEL in the most sensitive species. The dog is the most sensitive species and the NOAEL of 600 ppm (21 mg/kg bw/day) from the 6-month toxicity study in dogs was found to be suitable for setting an AOEL.

The absorption of tolclofos-methyl from the gastrointestinal tract was estimated to be >78% based on the excretion into urine in animals, thus absorption rate of 78% can be applied. Routine safety factor of 100 can be applied because no significant organ-specific toxicity or reproductive toxicity was evident.
Estimation of acceptable operator exposure using a safety factor of 100 leads to an AOEL for tolclofos-methyl of 0.16 (21 x 0.78/100) mg/kg bw/day.

$$\text{AOEL} = \frac{21 \text{ mg/kg bw/day} \times 78\%}{100} = 0.16 \text{ mg/kg bw/day}$$

B.6.10.10 Acute reference dose (ARfD)

Taking into account the low acute toxicity of tolclofos-methyl, establishment of an ARfD is not required.

B.6.10.11 Drinking water limit

The maximum admitted concentration, as established in the Directive 80/77/EC is 0.1µg/L.

B.6.11 Acute toxicity including irritancy and skin sensitization of preparations (Annex IIIA 7.1)

B.6.11.1 Acute oral toxicity in mice

Reference	: Segawa, T., 1981a	**Exposure**	: Single administration
Title of study	: Acute oral toxicity study of S-3349 50% wettable powder in mice	**Dose**	: 0, 1000, 2500, 5000 mg/kg bw
Test substance	: Tolclofos-methyl 50WP, batch No.: 11192, contents: 52.0% w/w, specification No. 12	**Vehicle**	:
Administration way	: Oral gavage	**GLP statement**	: No
Species	: ICR mice	**Guideline**	: In-house method, in accordance with 92/69/EEC, B1
Group size	: 10/sex/dose	**Acceptability**	: Yes
		LD_{50}	: >5000 mg/kg bw/day

Materials and methods

Tolclofos-methyl 50% wettable powder formulation was administered by single oral gavage to fasted groups of 10 male and 10 female ICR mice. The animals were observed for 14 days.

Findings

There were no mortalities during the study and the only symptoms observed were slight increases in spontaneous motor activity and in rearing immediately after administration of the preparation. Male animals on days 7 and 14 and female ones on day 7 were found to have lower body weight compared to the controls, at the highest dose of 5000 mg/kg bw (Table B.6.11.1-1). At necropsy, organs and tissues were grossly normal.

Table B.6.11.1-1: Acute oral toxicity of tolclofos-methyl 50% wettable powder formulation in mice: Body weight (g)

Dose	0 mg/kg bw	1000 mg/kg bw	2500 mg/kg bw	5000 mg/kg bw
Males				
Day 0	29.8	29.7	30.7	29.6
Day 7	34.1	33.1	34.8	27.6***
Day 14	35.3	36.2	35.8	33.0**
Females				
Day 0	25.8	24.8	24.2	24.1
Day 7	28.5	28.3	27.0	25.8***
Day 14	29.2	28.0	29.0	28.2

** *p < 0.01 in comparison with controls*
*** *p < 0.001 in comparison with controls*

Conclusions The oral LD_{50} value of tolclofos-methyl 50% wettable powder formulation is greater than 5000 mg/kg in mice.

B.6.11.2 Acute oral toxicity in rats

Reference	: Segawa, T., 1981b	**Exposure**	: 14 days
Title of study	: Acute oral toxicity study of S-3349 50% wettable powder in rats	**Dose**	: 0, 1000, 2500, 5000 mg/kg bw/day
Test substance	: Tolclofos-methyl 50WP, batch No.: 11192, contents: 52.0% w/w, specification No. 12	**Vehicle**	:
Administration way	: Oral gavage	**GLP statement**	: No
Species	: Sprague-Dawley rats	**Guideline**	: In house method, in accordance with 92/69/EEC, B1
Group size	: 10/sex/dose	**Acceptability**	: Yes
		LD_{50}	: >5000 mg/kg bw/day

Materials and methods

Tolclofos-methyl 50% wettable powder formulation was administered to fasted groups of 10 male and 10 female Sprague-Dawley rats. The animals were observed for 14 days.

Findings

There were no deaths at any of the dose levels administered. Slight increase in spontaneous motor activity was observed immediately and for 10 minutes after administration of 2500 or 5000 mg/kg bw, and slight sedation was observed 30 minutes after the administration. There were no differences in body weights. At necropsy, organs and tissues were grossly normal.

Conclusions The oral LD_{50} value of tolclofos-methyl 50% wettable powder formulation is greater than 5000 mg/kg bw in rats.
In accordance with the provisions of Council Directive 67/548/EEC and Directive 78/631/EEC, classification of tolclofos-methyl 50% wettable powder formulation is not required.

B.6.11.3 Acute dermal toxicity in mice

Reference	: Segawa, T., 1981c	**Exposure**	: Single exposure
Title of study	: Acute dermal toxicity study of S-3349 50% wettable powder in mice	**Dose**	: 0, 2500, 5000 mg/kg bw
Test substance	: Tolclofos-methyl 50WP, batch No.: 11192, contents: 52.0% w/w, specification No. 12	**Vehicle**	:
Administration way	: Dermal application	**GLP statement**	: No
Species	: ICR mice	**Guideline**	: In-house, in accordance with 92/69/EEC, B3
Group size	: 10/sex/dose	**Acceptability**	: Yes
		LD_{50}	: > 5000 mg/kg bw

Materials and methods

Tolclofos-methyl 50% wettable powder formulation was admimnistered dermally to ICR mice.

Findings

There were no deaths nor remarkable symptoms at any dose level, except that slight increase in spontaneous activity and preening was observed immediately after administration of 2500 or 5000 mg/kg bw and for approximately 1 hour. Body weights were comparable. At necropsy, organs and tissues were grossly normal.

Conclusions The dermal LD_{50} value of tolclofos-methyl 50% wettable powder formulation in mice was determined to be greater than 5000 mg/kg bw.

B.6.11.4 Acute dermal toxicity in rats

Reference	: Segawa, T., 1981d	**Exposure**	: Single exposure
Title of study	: Acute dermal toxicity study of S-3349 50% wettable powder in rats	**Dose**	: 0, 2500, 5000 mg/kg bw
Test substance	: Tolclofos-methyl 50WP (Batch No.: 11192, Contents: 52.0% w/w, Specification No. 12	**Vehicle**	:
Administration way	: Dermal application	**GLP statement**	: No
Species	: Sprague-Dawley rats	**Guideline**	: In-house, in accordance with 92/69/EEC, B3
Group size	: 10/sex/dose	**Acceptability**	: Yes

LD_{50}	: > 5000 mg/kg bw

Materials and methods

Tolclofos-methyl 50% wettable powder formulation was administered by single dermal application to groups of Sprague-Dawley rats.

Findings

There were no deaths nor remarkable symptoms at any dose level, except that slight hunchbacked posture in some animals was observed 30-60 minutes after administration of 2500 or 5000 mg/kg bw. Body weights were comparable. At necropsy, organs and tissues were grossly normal.

Conclusions The dermal LD_{50} value of tolclofos-methyl 50% wettable powder formulation in rats was determined to be greater than 5000 mg/kg bw.

In accordance with the provisions of Council Directive 67/548/EEC and Directive 78/631/EEC, classification of tolclofos-methyl 50% wettable powder formulation is not required.

B.6.11.5 Inhalation (rat)

Reference	:	**Exposure**	: 4 hours
Title of study	: An acute inhalation toxicity study of S-3349 50WP in the rat	**Dose**	: 13.3 mg/l
Test substance	: Tolclofos-methyl 50WP, batch No.: 5618, contents: 52.0% w/w, specification No. 12	**Vehicle**	:
Administration way	: Inhalation	**GLP statement**	: No
Species	: Sprague-Dawley rats	**Guideline**	: In-house method, in accordance with 92/69/EEC method B2
Group size	: 5/sex/dose	**Acceptability**	: Yes
		LC_{50}	: >13.3 mg/l

Materials and methods

Tolclofos-methyl 50% wettable powder formulation was administered by inhalation of a test atmosphere containing dust generated from the test material; single administration, whole body exposure

Findings

No death occurred during the 4-hour exposure or subsequent 14-day observation period. All rats appeared contaminated with the test material during the exposure period. Slight secretory increases (lachrymal, nasal and oral), piloerection and shallow breathing occurred during and immediately following exposure. These signs abated by the third day. There was no evidence of any residual or delayed toxicity at necropsy.

Conclusions No mortality was observed following 4-hour exposure by inhalation of tolclofos-methyl 50% wettable powder formulation. The LC_{50} value is estimated to be greater than 13.3 mg/l of the formulation (maximum concentration which can be tested).

In accordance with the provisions of Council Directive 67/548/EEC and Directive 78/631/EEC, classification of tolclofos-methyl 50% wettable powder formulation is not required.

B.6.11.6 Skin irritation

Reference	: Hara, S et al., 1981a	**Exposure**	: 24 hours, single administration
Title of study	: Primary eye and skin irritation tests of S.3349 50% water-dispersible powder in rabbits	**Dose**	: 0.5 g
Test substance	: Tolclofos-methyl 50WP, batch No.: 11192, contents: 52.0% w/w, specification No. 12	**Vehicle**	: Physiological saline
Administration way	: Skin	**GLP statement**	: No
Species	: New Zealand white rabbits	**Guideline**	: In-house method, in accordance with 92/69/EEC method B4
Group size	: 6/dose	**Acceptability**	: Yes
		Result	: Not irritant

Materials and methods

Tolclofos-methyl 50% wettable powder formulation was introduced on approximately 25.4 mm x 25.4 mm lint patches; each treatment was applied to two abraded and two intact areas of skin, then covered with an occlusive tape. Scoring of the treated skin was made at 24 and 72 hours and at day 7 in two intact and two abraded skin sites of each animal.

According to 92/69/EEC method B4, use of animals with abraded skin should be avoided.

Findings

Tolclofos-methyl 50% wettable powder formulation did not produce any irritating reactions such as erythema and oedema.

Conclusions In accordance with the criteria specified in Council Directive 67/548/EEC and Directive 78/631/EEC, tolclofos-methyl 50% wettable powder formulation is not classified as a skin irritant.

B.6.11.7 Eye irritation

Reference	: Hara, S et al., 1981a	**Exposure**	: Single administration
Title of study	: Primary eye and skin irritation tests of S.3349 50% water-dispersible powder in rabbits	**Dose**	: 0.1 g
Test substance	: Tolclofos-methyl 50WP, batch No.: 11192, contents: 52.0% w/w, specification No. 12	**Vehicle**	:
Administration way	: Skin	**GLP statement**	: No
Species	: New Zealand white rabbits	**Guideline**	: In-house method, in accordance with 92/69/EEC method B5
Group size	: Group 1: 6 Group 2: 3	**Acceptability**	: Yes
		Result	: Not irritant

Materials and methods

Tolclofos-methyl 50% wettable powder formulation was introduced into one eye of nine New Zealand White rabbits; the other eye served as a control. Examination of the test sites for ocular responses was made at 1, 24, 48, 72, 96 hours and 1 week after instillation.

Group I (6 rabbits): the treated eyes remained unwashed;

Group II (3 rabbits): the treated eyes were flushed for 1 min with ca. 300 ml lukewarm water 30 sec after application.

Findings

Tolclofos-methyl 50% wettable powder formulation did not produce any lesions in cornea of the treated eyes of the unwashed group, whereas slight congestion of iris was observed 24 hours after application (Table 6.11.7-1). Slight to moderate hyperaemia and slight chemosis and/or discharge in conjunctiva were also observed 1 to 48 hours after application. These changes disappeared by 72 hours after application in all animals. No ocular lesions were found in the washed eyes from 3 rabbits throughout the observation period.

Table B.6.11.7-1: Ocular reactions elicited by tolclofos-methyl 50% wettable powder in rabbits: unwashed group

	Cornea						**Iris**						**Conjunctiva**																	
													redness						**chemosis**						**discharge**					
time/rabbit	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**
1 h	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
24 h	0	0	0	0	0	0	1	0	1	0	0	1	1	1	2	1	1	1	1	0	1	1	0	1	0	0	0	1	0	0
48 h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
72 h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
96 h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1 week	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
mean score 24-72 h	0.00						0.17						0.50						0.22						0.06					

Conclusions On the basis of the eye reactions observed and the criteria specified in Council Directive 67/548/EEC and Directive 78/631/EEC, tolclofos-methyl 50% wettable powder formulation is not classified as an eye irritant.

B.6.11.8 Skin sensitization: Buehler test

Reference	: Hara, S et al., 1981b	**Exposure**	: Single administration
Title of study	: Skin sensitization test of S-3349 50% water-dispersible powder in guinea pigs	**Dose**	: 0.5 g
Test substance	: Tolclofos-methyl 50WP, batch No.: 11192, contents: 52.0% w/w, specification No. 12	**Vehicle**	:
Administration way	: Skin	**GLP statement**	: No
Species	: New Zealand white rabbits	**Guideline**	: In-house method, in accordance with 92/69/EEC method B6
Group size	: Group 1: 6 Group 2: 3	**Acceptability**	: Yes
		Result	: Not sensitizising

Materials and methods

Tolclofos-methyl 50% wettable powder formulation slightly moistened with distilled water was placed on 3.8 cm × 3.8 cm lint patch then applied to the back of the animals under an occlusive tape for 24 hours. Ten induction applications were performed with intervals of 2 or 3 days. The treated animals were challenged topically for 24 hours (same dose level as during the induction), two weeks after the last sensitization application. The control animals were treated similarly with the exception that the test compound was omitted from the induction applications. In the positive control group, 0.5% DNCB (2,4-dinitrochlorobenzene) was tested in the same manner as the test material.

The challenge site was evaluated 24 hours after the challenge.

More inductions were performed than required.

Findings

No allergic reaction was observed in the animals treated with tolclofos-methyl 50% wettable powder formulation as well as in the negative control animals. In the positive control, slight to severe erythema and swelling were observed.

Conclusions It is suggested from these results that tolclofos-methyl 50% wettable powder formulation is not a skin sensitizer.

In accordance with the provisions of Council Directive 67/548/EEC and Directive 78/631/EEC, classification of tolclofos-methyl 50% wettable powder formulation is not required.

B.6.11.9 Summary of acute toxicity including irritancy and skin sensitization of preparations

Study	Dose levels	Results
Segawa, 1981a Acute oral toxicity study of S-3349 50% wettable powder in mice	1000, 2500, 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw
Segawa, 1981b Acute oral toxicity study of S-3349 50% wettable powder in rats	1000, 2500, 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw
Segawa, 1981c Acute dermal toxicity study of S-3349 50% wettable powder in mice	2500, 5000 mg/kg bw	LD_{50} > 1000 mg/kg bw
Segawa, 1981d Acute dermal toxicity study of S-3349 50% wettable powder in rats	2500, 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw No effect on cholinesterase levels
Eschbach, Hogan, 1981 An acute inhalation toxicity study of S-3349 50WP in the rat	13.3 mg/l	LC_{50} > 13.3 mg/l
Hara, 1981a Primary eye and skin irritation tests of S.3349 50% water-dispersible powder in rabbits	0.5g (skin irritation test), 0.1 g (eye irritation test)	Not irritant
Hara, 1981b Skin sensitization test of S-3349 50% water-dispersible powder in guinea pigs	0.5 g	Not sensitizising

Tolclofos-methyl 50% wettable powder formulation has low acute toxicity when administered orally, dermally and via inhalation to rats. It is not a skin or eye irritant, nor a skin sensitizer.

B.6.12 Dermal absorption (Annex IIIA 7.3)

B.6.12.1 Dermal absorption, *in vivo* in the rat

Reference	: Savides, M.C., 2003	**Exposure**	: 6 h (16 rats per dose) or 24 h (4 rats per dose)
Title of study	: [^{14}C]Tolclofos-methyl 50% SC: *In vivo* dermal absorption in male Sprague-Dawley rats	**Dose**	: 0.04 or 25 mg a.s./50 µL/10 cm^2/rat
Test substance	: [phenyl-^{14}C]tolclofos-methyl, batch No.: CP-2712, radiochemical purity: 98.5%, specific radioactivity: 12.4 MBq/mg, unlabelled tolclofos-methyl, batch No.: 000427G, purity: 99.7%, tolclofos-methyl 50SC blank formulation, batch No.: SBM02/050/01	**Vehicle**	: Water
Administration way	: Dermal	**GLP statement**	: Yes
Species	: Sprague-Dawley rats	**Guideline**	: Draft OECD 427 (2002)
Group size	: 20/dose	**Acceptability**	: Yes
		Result	:

Materials and methods

A formulation of [phenyl-^{14}C]tolclofos-methyl was prepared by mixing ^{14}C-labeled with unlabelled tolclofos-methyl, tolclofos-methyl 50SC blank formulation and/or deionized water at the appropriate rate [High dose (Concentrate): 500 g a.s./L, Low dose (1:625 v/v spray dilution): 0.8 g a.s. /L]. After each exposure period, the application site skins of rats were washed with soapy water and water. Four rats were terminated at the end of the 6- and 24-hour application periods. The remaining rats (washout groups) were returned to their metabolism cages. Four rats per dose level were terminated at 48, 72 and 168 hours postdose. The excreta (urine and feces) were collected during the entire exposure and washout periods. At termination, the rats were sacrificed to remove blood and treated skin and the carcass was retained. Furthermore, the *stratum corneum* was removed from the treated skin by tape stripping. Amounts of ^{14}C in urine, feces, *stratum corneum*, remaining skin, residual carcass, skin wash (soapy water and water), protective device and cage-wash, were determined.

Findings

1. Systemic absorption of radiolabel

Systemic absorption of radiolabel expressed as a percent of the applied dose (%AD) is summarized in Table B.6.12.1-1.

Table B.6.12.1-1: Dermal absorption, *in vivo* in rats: Systemic absorption of radiolabel (expressed as %AD)

Exp. (hr) *1	Term (hr) *2	Low Dose (0.004 mg/cm^2)					High Dose (2.5 mg/cm^2)				
		Urine	Cage-Wash	Feces	Carcass	Abs. *3	Urine	Cage-Wash	Feces	Carcass	Abs. *3
6	6	5.12	2.97	0.05	3.11	11.59	0.04	0.12	0.03	0.60	0.78
24	24	39.99	5.47	0.52	1.98	48.08	0.21	0.05	0.00	0.00	0.26
6	48	14.62	3.29	0.42	0.08	18.41	0.35	0.04	0.00	0.04	0.43
6	72	13.93	3.70	0.49	0.22	18.34	0.47	0.08	0.00	0.00	0.56
6	168	16.72	2.25	0.33	0.00	19.33	0.37	0.05	0.05	0.00	0.46

**1: Exposure period, *2: Termination period, *3: Systemic Absorption*

Urine:

Most of the radiolabel that was absorbed was excreted via the urine. At the low dose, 0.004 mg/cm^2, about 5.2% and 40.0% AD were excreted in the urine following exposure and termination at 6 and 24 hours, respectively. In the case of the animals exposed for 6 hours, washed at that time point and maintained until 48, 72 or 168-hours postdose (washout groups), about 13.9 to 16.7% AD was excreted in the urine. These data demonstrate that the washing of the skin at 6-hours postdose prevented further absorption of the compound. At the high dose, 2.5 mg/cm^2, less than 0.5% AD was excreted in the urine. Washing of the skin after this applied dosage did not appear to have an effect on decreasing further absorption of radiolabel.

Cage wash:

Less than 5.5% and 0.12% AD was detected in the cage washes of the low and high dose groups, respectively.

Feces:

Very little of the radiolabel that was absorbed was excreted via the feces.

Blood and Carcass:

Detectable amounts of radiolabel were only found in the blood of the 6-hour and 24-hour low dose groups (non-washout groups, ≤ 0.27% AD and ≤ 0.16 % AD, respectively) with one exception: a low dose, 168-hour termination animal had 0.11% AD in the blood. Little to no radiolabel remained in the carcass of the rats from the washout group by 48-hours postdose.

Systemic absorption:

Following application of the low dose of [phenyl-^{14}C]tolclofos-methyl, systemic absorption of radiolabel increased from about 12% AD by the 6-hour exposure to about 48% AD by the 24-hour exposure. Washing of the skin at 6-hours postdose had a dramatic effect in eliminating further systemic absorption, since absorption averaged only about 18-19% in all the low dose animals whose skin was washed 6-hours postdose. Systemic absorption following the high dose was low and it was difficult to determine the effect of washing the skin at 6-hours postdose on the systemic absorption. Less than 0.8% AD was absorbed systemically following the high dose of tolclofos-methyl.

2. Radiolabel remaining in/on washed skin

Skin fractionation was performed to further define the localization of the test substance within the skin. The amount of radiolabel remaining in/on the treated skin after it was washed is the sum of the material in the *stratum corneum* (stripped skin) and that of the skin remaining after the skin stripping procedure. These results are detailed in Table B.6.12.1-2.

Table B.6.12.1-2: Dermal absorption, *in vivo* in rats: Radiolabel remaining in/on the washed skin (expressed as %AD)

Exp. (hr)[*1]	Term (hr)[*2]	Low Dose (0.004 mg/cm^2)			High Dose (2.5 mg/cm^2)		
		Stratum Corneum	Remaining Skin	Total in/on skin	*Stratum Corneum*	Remaining Skin	Total in/on skin
6	6	4.72	2.03	6.75	0.35	0.17	0.51
24	24	1.56	0.84	2.40	0.27	0.14	0.41
6	48	0.64	0.05	0.69	0.07	0.01	0.07
6	72	0.69	0.03	0.72	0.03	0.00	0.00
6	168	0.61	0.02	0.63	0.00	0.00	0.00

*[*1]: Exposure period, [*2]: Termination period*

Non-absorbed dose

The portion of the dose classified as "non-absorbed" included the skin washes and dose that was found on the protective device. These data are summarized in Table B.6.12.1-3. In all but one case (low dose, 24-hour exposure group), the majority of the dose that was not absorbed was removed from the skin with the skin washes.

Table B.6.12.1-3: Dermal absorption, *in vivo* in rats: Radiolabel not absorbed (expressed as %AD)

Exp. (hr)[*1]	Term (hr)[*2]	Low Dose (0.004 mg/cm^2)			High Dose (2.5 mg/cm^2)		
		Skin wash	Protective device	Total not absorbed	Skin wash	Protective device	Total not absorbed
6	6	64.23	7.79	72.02	89.57	2.05	91.62
24	24	17.52	22.28	39.80	87.65	3.80	91.45
6	48	66.24	5.79	72.03	93.15	1.24	94.39
6	72	65.36	5.64	71.00	90.27	2.26	92.54
6	168	65.73	4.28	70.00	90.11	2.20	92.30

*[*1: Exposure period, [*2]: Termination period*

Recovery of applied dose

The recoveries of applied radiolabel in the individual animals was 91.8 ± 2.3%, which indicated acceptable material balance (Table B.6.12.1-4).

Table B.6.12.1-4: Dermal absorption, *in vivo* in rats: Recovery of applied radiolabel (expressed as %AD)

Exp (hr)[*1]	Term (hr)[*2]	Low Dose (0.004 mg/cm^2)	High Dose (2.5 mg/cm^2)
6	6	90.36	92.91
24	24	90.28	92.11
6	48	91.12	94.89
6	72	90.06	93.12
6	168	89.96	92.77

*[*1]: Exposure period, [*2]: Termination period*

Conclusions

Following a dermal dose of [phenyl-^{14}C]tolclofos-methyl at concentrations of 0.004 or 2.5 mg/cm^2, the radiolabeled material was absorbed and excretion was primarily via the urine.

In the low dose groups, systemic absorption increased from about 12% AD by the 6-hour exposure to about 48% AD by the 24-hour exposure. Washing of the skin at 6-hours postdose had a dramatic effect in eliminating further systemic absorption, since absorption averaged only about 18-19% in all the low dose animals whose skin was washed 6-hours postdose. The amount of the applied radiolabel remaining in/on the skin decreased with time. Most of the radiolabel was associated with the *stratum corneum*. In the animals whose skin was washed at 6-hours postdose, $\leq$ 0.72% AD was in/on the skin when terminated at 48, 72 or 168 hours postdose. The amount of material remaining in the skin following removal of the *stratum corneum* was negligible in the three washout groups.

In the high dose groups, systemic absorption was more variable, due to the very low excretion of radiolabel in the washout groups. Due to this variability, no inference could be made on the effectiveness of washing the skin on further absorption. Systemic absorption at the high dose was about 0.8% or less of the applied radiolabel. The amount of the applied dose that remained in/on the skin peaked at about 24 to 48 hours postdose. As was the case with the low dose animals, the majority of the radiolabel was associated with the *stratum corneum* (except for the 6-hour exposure time).

B.6.12.2 Comparative dermal absorption, *in vitro* using rat and human skin

Reference	: Ward, R.J., 2003	**Exposure**	: 24 h
Title of study	: Tolclofos-methyl 500g/l SC formulation: *In vitro* absorption of tolclofos-methyl through human and rat epidermis	**Dose**	: 500 g a.s./L and as a 1:625 v/v (nominally ≡ 0.8 g a.s./L) spray strength dilution
Test substance	: [phenyl-^{14}C]tolclofos-methyl, batch No.: CP-2712, radiochemical purity: 98.5%, specific radioactivity: 12.4 MBq/mg), unlabelled tolclofos-methyl, batch No.: 000427G, purity: 99.7%, tolclofos-methyl 50SC blank formulation, batch No.: SBM02/050/01	**Vehicle**	: Water
Administration way	: In vitro	**GLP statement**	: Yes
Species	: Rat and human skin	**Guideline**	: Draft OECD 428 (2002)
Group size	: 6/dose	**Acceptability**	: Yes
		Result	:

Materials and methods

The formulation was applied as preparations representing the commercial concentrate formulation and as a spray strength dilution of the formulation in water. The absorption process was followed using [phenyl-^{14}C]tolclofos-methyl, which was incorporated into the formulation and dilution prior to application. A glass diffusion cell, which has an exposed membrane area of 2.54 cm^2 was used in this study. Discs of approximately 3.3 cm diameter of prepared epidermal membrane from at least three subjects/animals were mounted, dermal side down, in diffusion cells held together with individually numbered clamps. The receptor chambers of the cells, containing small magnetic stirrer bars, were filled with a recorded volume of receptor fluid (50% ethanol in distilled water) and placed in a water bath maintained at normal skin temperature of 32 ± 1°C. The concentrate formulation and the spray strength dilution were applied to 5 to 6 epidermal membranes at a rate of 10 µl/cm^2. . At 0 (pre-dose), 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours after application, 100 µl samples of the receptor fluid were taken for analysis. The volume of fluid in the receptor chamber was maintained by the addition of 100 µl fresh receptor fluid to the chamber immediately after the removal of each sample. The surface of the epidermis was subjected to a washing procedure at 6 hours after application and again at the end of the 24-hour exposure period. Rat epidermal membranes were digested in Soluene 350. In the case of human epidermis, the *stratum corneum* was removed by tape stripping before the remaining epidermis was digested. Radioactivity in receptor fluid, skin washes, epidermal membranes and *stratum corneum* was determined by liquid scintillation counting after digestion or extraction where necessary.

Findings

1. Human epidermis

Absorption data (Table B.6.12.2-1)

Concentrate formulation:

Absorption of tolclofos-methyl from the concentrate formulation maintained an essentially constant rate (0.072 µg/cm^2/h) over the entire 24 hour exposure period. Amounts of tolclofos-methyl absorbed during a typical working day (ie. 6-10 hours) varied between 0.392 µg/cm^2 (0.008% of dose) at 6 hours to 0.872 µg/cm^2 (0.017%) at 10 hours, with a total of 1.66 µg/cm^2 (0.033%) being absorbed by 24 hours.

1:625 v/v spray strength dilution:

The fastest rate of tolclofos-methyl absorption from this application was during the first 6 hours of exposure (0.029 µg/cm^2/h). After this time, the rate slowly reduced to give a rate over a typical 10 hour working day period of 0.024 µg/cm^2/h. The rate over the entire 24 hour exposure period was 0.016 µg/cm^2/h. In terms of amount and percent of dose absorbed during periods typical of a working day, tolclofos-methyl absorption varied between 0.175 µg/cm^2 (2.18% of dose) at 6 hours to 0.234 µg/cm^2 (2.91%) at 10 hours, with a total of 0.373 µg/cm^2 (4.63%) being absorbed by the end of the experiment at 24 hours.

Table B.6.12.2-1: Dermal absorption, *in vitro*: Dermal absorption through human epidermis (n=6)

Test Materials	Time (hr)	Amount (µg/cm^2)	Percent absorbed (%)	Absorption rate (µg/cm^2/h)
Concentrate (500 g/L), 5000 µg/cm^2	6	0.392	0.008	0.072 (0 – 24 hr)
	8	0.745	0.015	
	10	0.872	0.017	
	24	1.66	0.033	
1:625 v/v spray strength dilution (0.8 g/L), 8 µg/cm^2	6	0.175	2.18	0.029 (0 – 6 hr) 0.024 (0 – 10 hr) 0.016 (0 – 24 hr)
	8	0.206	2.56	
	10	0.234	2.91	
	24	0.373	4.63	

Mass Balance Data (Table B.6.12.2-2)

Concentrate formulation: The majority of the applied tolclofos-methyl (93.4%) was removed by the skin washing procedure at 6 hours, with a further 1.17% being washed off at 24 hours. The proportion recovered from the *stratum corneum* (represented by the tape strips) was 0.049%, with a further 0.092% being recovered from the remaining epidermis.

1:625 v/v spray strength dilution: The skin washing procedure at 6 hours accounted for the highest proportion of recovered tolclofos-methyl (mean 82.2% of dose), with a further 3.94% being recovered from the washings at 24 hours. The proportion recovered from the *stratum corneum* was 1.57% of the dose, with a further 0.270% being extracted from the remaining epidermis.

Table B.6.12.2-2: Dermal absorption, *in vitro*: Distribution of radiolabel in human epidermis study (% of applied radiolabel)

Test Compartment	Concentrate (500 g/L), 5000 µg/cm^2	1:625 v/v spray strength dilution (0.8 g/L), 8 µg/cm^2
Spreader	2.40	3.88
Donor Chamber	0.464	1.47
Skin Wash at 6 hr	93.4	82.2
Skin Wash at 24hr	1.17	3.94
Stratum Corneum	0.049	1.57
Remaining Epidermis	0.092	0.270
Absorbed	0.033	4.63
Total	97.6	97.9

2. Rat Epidermis

Absorption data (Table 6.12.2-3)

Concentrate formulation: Tolclofos-methyl absorption from the concentrate formulation through rat epidermis was fastest during the first half of the exposure period (0-10 hour rate = 3.45 µg/cm^2/h). Absorption in the latter period reduced to give an overall rate of 2.63 µg/cm^2/h for the entire 24-hour exposure period. As with human epidermis, the skin washing process at 6 hours after application does not appear to have significantly affected the overall rate, however the absorption profile indicates a slight decrease in rate between 4-6 hours (ie. immediately prior to the washing), followed by a temporary increase in rate between 6-8 hours. In terms of amount and percent of dose absorbed during periods typical of a working day (ie. 6-10 hours), tolclofos-methyl absorption

varied between 16.3 µg/cm^2 (0.326% of dose) at 6 hours to 33.9 µg/cm^2 (0.679%) at 10 hours, with a total of 60.6 µg/cm^2 (1.21%) being absorbed by the end of the experiment at 24 hours.

1:625 v/v spray strength dilution: The fastest rate of tolclofos-methyl absorption from the spray dilution occurred during the first 4 hours of exposure (1.03 µg/cm^2/h). After this time, the rate rapidly reduced, so that by 10 hours the absorption process had effectively ceased, giving an average 0-10 hour rate of 0.529 µg/cm^2/h. Such a rapid decrease in rate indicates that the reservoir of available penetrant has depleted and is a reflection of the very small amount of tolclofos-methyl applied (8 µg/cm^2), rather than other rate limiting effects, such as solubility in the receptor fluid. This is supported by the amounts of tolclofos-methyl absorbed at time points representing typical working day lengths, where tolclofos-methyl absorption varied between 4.96 µg/cm^2 (61.4% of dose) at 6 hours to 5.67 µg/cm^2 (70.2%) at 10 hours, with a total of 6.21 µg/cm^2 (76.9%) being absorbed by the end of the experiment at 24 hours.

Table B.6.12.2-3: Dermal absorption, *in vitro*: Dermal absorption through rat epidermis

Test Materials	Time (hr)	Amount (µg/cm^2)	Percent absorbed (%)	Absorption rate (µg/cm^2/h)
Concentrate (500 g/L), 5000 µg/cm^2	6	16.3	0.326	3.45 (0 – 10 hr) 2.63 (0 – 24 hr)
	8	29.6	0.593	
	10	33.9	0.679	
	24	60.6	1.21	
1:625 v/v spray strength dilution (0.8 g/L), 8 µg/cm^2	6	4.96	61.4	1.03 (0 – 4 hr), 0.529 (0 – 10 hr)
	8	5.44	67.4	
	10	5.67	70.2	
	24	6.21	76.9	

Mass Balance Data (Table B.6.12.2-4)

Concentrate formulation: The vast majority of the applied tolclofos-methyl (89.8%) was removed by the skin washing procedure at 6 hours, with a further 2.04% being washed off at 24 hours. The proportion recovered from the whole epidermis was 0.381%.

1:625 v/v spray strength dilution: As detailed above in the absorption data the absorbed proportion of applied tolclofos-methyl was very high (76.9%), consequently, the amount washed from the surface of the skin at 6 hours was relatively low (15.7%), with a further 2.16% removed at 24 hours. The proportion recovered from the whole epidermis was 3.27%.

Table B.6.12.2-4:Dermal absorption, *in vitro*: Distribution of radiolabel in rat epidermis study (% of applied radiolabel)

Test Compartment	Concentrate (500 g/L), 5000 µg/cm^2	1:625 v/v spray strength dilution (0.8 g/L), 8 µg/cm^2
Spreader	2.30	3.44
Donor Chamber	0.330	0.496
Skin Wash at 6 hr	89.8	15.7
Skin Wash at 24hr	2.04	2.16
Epidermis	0.381	3.27
Absorbed	1.21	76.9
Total	96.1	102

Conclusions The absorption of tolclofos-methyl through rat epidermis over-predicts absorption through human epidermis by up to approximately 50 times, based upon absorption rate. In the event of human skin contact with either the formulation concentrate or the 1:625 v/v spray strength dilution, over 80% of the tolclofos-methyl is likely to be removed from the surface of the skin by normal washing procedures. The small residual amounts of tolclofos-methyl found in human skin, especially that recovered from the *stratum corneum*, is most likely to be lost by desquamation *in vivo*. These data predict that the dermal absorption of tolclofos-methyl from potential exposure to this SC formulation would be minimal.

B.6.12.3 Summary and conclusions on dermal absorption

***In vivo* Dermal absorption**

Following a dermal dose of [phenyl-^{14}C]tolclofos-methyl at concentrations of 0.004 or 2.5 mg/cm^2, the radiolabeled material was absorbed excreted primarily via the urine.

In the low dose groups, systemic absorption increased from about 12% AD by the 6-hour exposure to about 48% AD by the 24-hour exposure. Washing of the skin at 6-hours postdose had a large effect in eliminating further systemic absorption, since absorption averaged only about 18-19% in all the low dose animals whose skin was washed 6-hours postdose. The amount of the applied radiolabel remaining in/on the skin decreased with time. Most of the radiolabel was associated with the *stratum corneum*. In the animals whose skin was washed at 6-hours postdose, $\leq$ 0.72% AD was in/on the skin when terminated at 48, 72 or 168 hours postdose. The amount of material remaining in the skin following removal of the *stratum corneum* was negligible in the three washout groups.

In the high dose groups, systemic absorption was more variable, due to the very low excretion of radiolabel in the washout groups. Due to this variability, no inference could be made on the effectiveness of washing the skin on further absorption. Systemic absorption at the high dose was about 0.8% or less of the applied radiolabel. The amount of the applied dose that remained in/on the skin peaked at about 24 to 48 hours postdose. As was the case with the low dose animals, the majority of the radiolabel was associated with the *stratum corneum* (except for the 6-hour exposure time).

The radioactivity remaining in skin after the 6-hour wash seems to have been absorbed and excreted over the remaining period of the experiment. The sum of the radioactivity systemically absorbed plus the amount in skin at any time point is therefore equal to the amount that will ultimately be absorbed. The mean of the values obtained for 6, 48, 72 and 168 hours is a better estimate of the absorption than would be obtained from just one timepoint; these values are shown below and have been used later for the calculation of human absorption *in vivo*.

Time (h)	Low Dose				High Dose			
	Systemic absorption (%)	Dose remaining in/on skin (%)	Total (%)	Mean (%)	Systemic absorption (%)	Dose remaining in/on skin (%)	Total (%)	Mean (%)
6	11.59	6.75	18.34	19.12	0.78	0.51	1.29	0.71
48	18.41	0.69	19.10		0.43	0.07	0.50	
72	18.34	0.72	19.06		0.56	0.03	0.59	
168	19.33	0.63	19.96		0.46	0.00	0.46	

***In vitro* Dermal absorption**

The absorption of tolclofos-methyl through rat epidermis over-predicts absorption through human epidermis by up to approximately 50 times, based upon absorption rate. In the event of human skin contact with either the formulation concentrate or the 1:625 v/v spray strength dilution, over 80% of the tolclofos-methyl is likely to be removed from the surface of the skin by normal washing procedures. The small residual amounts of tolclofos-methyl found in human skin, especially that recovered from the *stratum corneum*, is likely to be lost by desquamation *in vivo*, though, for the purposes of the operator exposure calculations it has been assumed that this will be absorbed. These data predict that the dermal absorption of tolclofos-methyl from potential exposure to this SC formulation would be minimal.

Estimation of *in vivo* human absorption rate

In vivo human absorption rate (%) was calculated by the following equation:

In vivo human absorption rate (%) = *In vivo* rat absorption rate (%) x
In vitro human maximum flux value (µg/cm^2/h) / *In vitro* rat maximum flux value (µg/cm^2/h)

The appropriate values are taken from the following table.

Type of study	Species	Dose range tested	Result	Reference
Dermal absorption *in vivo*	**Rat**	**Low Dose (1:625 v/v spray dilution):** 0.004 g/cm^2 **High Dose (concentrate):** 2.5 mg/cm^2	**Dermal Absorption Rate** **Low dose (worst case except for 24 hr exposure group): 19.12%** **High dose (worst case except for 24 hr exposure group): 0.71%**	Savides, M.C., 2003 (QM-0057)
Dermal absorption *in vitro*	**Rat**	**Low Dose (1:625 v/v spray dilution):** 0.08 g/cm^2 , **High dose (concentrate):** 5 mg/cm^2	**Maximum Flux Value** **Low dose:** 1.03 µg/cm^2/h (0 – 4 hr) **High dose:** 3.45 µg/cm^2/h (0 – 24 hr)	Ward, R.J., 2003 (QM-0056)
	Human	**Low Dose (1:625 v/v spray dilution):** 0.08 g/cm^2 , **High dose (concentrate):** 5 mg/cm^2	**Maximum Flux Value** **Low dose:** 0.029 µg/cm^2/h (0 – 6 hr) **High dose:** 0.072 µg/cm^2/h (0 – 24 hr)	

Therefore, *in vivo* human absorption rate for spray dilution and concentrate were estimated to 0.538% (=19.12 x 0.029 / 1.03) and 0.015% (= 0.71x 0.072 / 3.45), respectively.

B.6.13 Toxicological data on non active substances (Annex IIIA 7.4 and point 4 of the introduction)

No toxicological data are received from the manufacturers of the formulants other than those described in the Safety Data Sheets.

B.6.14 Exposure data (Annex IIIA 7.2)

B.6.14.1 Operator exposure

Tolclofos-methyl (WP/SC formulation containing 50% tolclofos-methyl or dust formulation containing 10% tolclofos-methyl) is used to control *Rhizoctonia solani* in soil in which potatoes and lettuce are planted. For potatoes the SC formulation may be applied to seed potatoes using misting equipment on a roller table or by in-furrow spraying at the time of planting. The dust formulation containing tolclofos-methyl may be added to potatoes in the hoppers of planters or to potatoes in seed dusting machines. For lettuce grown in glasshouses, tolclofos-methyl 50WP is applied to and then incorporated into the soil prior to sowing or transplantation. In glasshouses, tolclofos-methyl 50WP is applied using hand-held sprayers and automatic spray equipment.

The methods used for estimating/measuring exposure to tolclofos-methyl and the application equipment used to apply tolclofos-methyl is identified below.

Crop	Application equipment	Method/study
(1) Potatoes (field)	(1A)Misting equipment with hydraulic nozzles or Mantis Mafex® mounted on roller table (1B)Treatment with dust in the hopper of planter (1C) In-furrow spraying at time of planting (1D) Seed dusting machines	(1A) B.6.14.1.1.1 Estimation of exposure using a field study on roller tables (1B) B.6.14.1.1.2 Estimation of exposure using a field study with dusting machines and related activities (1C) B.6.14.1.1.3 Estimation of exposure using the UK POEM and German models (1D) B.6.14.1.1.4 Measurement of exposure to dust formulation
(2) Lettuce (glasshouse)	(2A) Automatic spray equipment (2B) Hand-held sprayer	(2A and B) B.6.14.1.2.1

The estimates of total tolclofos-methyl were calculated as a proportion of the proposed AOEL for the active ingredient. These estimates are presented in the respective studies.

The UK POEM[1] (Predictive operator exposure model) and the German model[2] do not contain data with which to estimate exposures for operators of misting equipment mounted on rolling tables, or for potato seed treatment with a dust formulation. However, operator exposures can be estimated based on a surrogate study for similar roller table spray applications to seed potatoes, and the estimated operator exposures based on this study are presented in B.6.14.1.1.1. Operator exposures for potato seed treatment with a dust formulation have been measured (study summarized in B.6.14.1.1.4). Moreover, operator exposures for seed dusting machines and related activities can be estimated based on a surrogate study involving treatment with a different product, and the resulting operator exposures are presented in B.6.14.1.1.2. The estimations using the UK POEM and German models are presented in B.6.14.1.1.3 (potatoes) and in B.6.14.1.2.1 (lettuce).

[1] Scientific Subcommittee on Pesticides and British Agrochemicals Joint Medical Panel., Estimation of Exposure and Absorption of Pesticides by Spray Operators (UK MAFF) 1986 and the Predictive Operator Exposure Model (POEM – UK MAFF) 2003

[2] Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protection); Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Berlin-Dahlem, no. 277, 1992

B.6.14.1.1 Potatoes

B.6.14.1.1.1 Estimation for operator exposure for spray application to potatoes on roller tables

Reference	: Lloyd, G. et al., 1980
Title of study	: Evaluation of operator hazards – ULV application of thiabendazole to potatoes on harvesting equipment
Test substance	: "Storite" (45% thiabendazole)
Guideline	: In-house method
GLP	: No
Acceptability	: Yes

Materials and methods

Operator exposure data on the application of tolclofos-methyl to seed potatoes using misting equipment mounted over a roller table are not available. However, data from an operator exposure study, "Evaluation of Operator Hazards - ULV Application of Thiabendazole to Potatoes on Harvesting Equipment," can be used as a surrogate to estimate operator exposures to tolclofos-methyl.

This study measured exposures to operators using a Mantis Matex 79 sprayer mounted on a roller table. Particular attention was paid to contamination of the hands of workers sorting sprayed potatoes. The sprayer was supported by a steel frame which was bolted onto the delivery section of a mechanical elevator system. A side curtain surrounded the Mantis unit to reduce exposure. The rotary atomiser, dosing pump and liquid chemical were attached to the top of the framework, and a plastic curtain covered the unit on all sides. The atomiser was set to deliver 90 ml "Storite" (45% thiabendazole) per tonne of potatoes at a spray treatment rate of 6 tonne/hr.

One operator and two observers wearing special clothing and modified respirators occupied positions around the spraying unit in positions occupied during normal practice. The study participants did not wear gloves, and the respirators were modified to allow inhalation sample collection. Potatoes were handled at random by the operator and observers in order to measure exposures associated with sorting treated potatoes. Additional air sampling equipment was placed around the spraying unit. The spray droplet size spectrum was determined by placing magnesium oxide coated slides on a tray conveyed through the spray unit and determining the size distribution using a Zeiss Particle Size Analyser.

Findings

The measured potential dermal and inhalation exposures are summarised in the tables below. Dermal exposures to hands were observed to be influenced by the number of potatoes handled per hour. Otherwise, dermal exposures to the body of the operator and observers were comparable. Aerosol particles escaping through gaps in the side curtain and base of the Mantis unit explain the observed inhalation exposures.

Table B.6.14.1.1.1-1: Measured potential inhalation exposures

Sample	mg as/m^3
A (air sampler)	0.16
B (air sampler)	0.06
C (air sampler)	0.02
D (air sampler)	0.01
E (air sampler)	0.13
F (air sampler)	0.04
G (air sampler)	0.03
X (human sampler)	0.11
Y (human sampler)	0.05
Z (human sampler)	0.05

Table B.6.14.1.1.1-2: Measured dermal exposures (mg as/hr)

Sample	On body surface (excluding hands)						Hands [1]
	Head/neck	Trunk	Arms	Thighs	Legs	Total	
Operator (Y)	0.6	6.6	<0.5 [2]	3.3	5.1	<16.1	6.6
Observer (X)	<0.4	4.5	<0.5	9.8	2.4	<17.6	10.0
Observer (Z)	<0.4	5.1	<0.5	6.5	3.6	<16.1	22.5

[1] Number of potatoes handled per hour: Y = 110, X = 35, Z = 174.
[2] "<" indicates non-detect at the indicated detection limit.

Data used for the calculations

The data reported in the above summarized operator exposure study were used to estimate generic dermal and inhalation unit exposures for operators of misting equipment mounted over a roller table.

Dermal exposures measured in the thiabendazole operator exposure study were reported in units of mg as/hr. To express these exposures in the desired units of mg/kg as, the following conversion factors were used:

Crop	Processing rate	Application rate
Potatoes (field)	In the thiabendazole operator exposure study, potatoes were processed at a rate of 6 tonnes/hr	The application rate in the thiabendazole operator exposure study was 90 ml/tonne of a formulation containing 45% active substance, which corresponds to an application rate of 0.0405 kg as/tonne.

Dermal exposures (mg as/h) reported in the operator exposure study were divided by [6 tonnes/h × 0.0405 kg as/tonne = 0.243 kg as/h] to express the exposures in units of mg/kg as. Table B.6.1.4.1.1.1-3 illustrates the calculation of generic dermal unit exposures for operators of misting equipment mounted over a roller table.
As an example calculations for operator Y are as follows:
Dermal exposure (body) from the thiabendazole study (Lloyd et al. 1980) was 15.85 mg as/h. Amount of product handled/h as calculated above = 0.243 kg as/h.
The dermal unit exposure (body) is thus 15.85 mg as/h / 0,243 kg as/h = 65.22 mg/kg as.
The dermal exposure (hands) from the thiabendazole study (Lloyd et al. 1980) was 6.6 mg as/h. The dermal unit exposure (hands) is thus 6.6 mg as/h / 0.243 kg as/h = 27.16 mg/kg as.

Table B.6.14.1.1.1-3: Estimation of dermal unit exposures from dermal exposures reported in a thiabendazole operator exposure study for misting equipment mounted over a roller table

	Dermal exposure, Body [from the thiabendazole operator exposure study] (mg as/hr)	Dermal unit exposure, Body (mg/kg as)	Dermal exposure, Hands [from the thiabendazole operator exposure study] (mg as/hr)	Dermal unit exposure, Hands (mg/kg as)
Operator Y	15.85	65.22	6.6	27.16
Observer X	17.15	70.58	10.0	41.15
Observer Z	15.65	64.40	22.5	92.59

Assuming a worst case, generic unit dermal exposures for observer Z were used to estimate dermal exposures to tolclofos-methyl associated with operating misting equipment mounted over a roller table.

Inhalation exposures measured in the operator exposure study were reported in units of mg/m^3. Ten inhalation samples were collected, with reported concentrations ranging from 0.02 to 0.16 mg as/m^3 (see Table 6.14.1.1.1-1 above). To express these reported inhalation exposures in the desired units of mg/kg as, the following conversion factors were used:

The inhalation rate was assumed to be 29 l/min, which corresponds to 1.74 m^3/h. Inhalation exposures (mg/m^3) reported in the thiabendazole operator exposure study were multiplied by the inhalation rate [1.74 m^3/hr] and divided by the factor [6 tonnes/h × 0.0405 kg as/tonne = 0.243 kg as/h] to express inhalation exposures in units of mg/kg as. Assuming a worst case and thus using data from X (human sampler) in Table B.6.14.1.1.1-1inhalation exposure was calculated to be [0.11 mg/m^3 x 1.74 m^3/h / (6 tonnes/h x 0.0405 kg as/tonne) = 0.79 mg/kg as]. This unit exposure was used to estimate inhalation exposures to tolclofos-methyl associated with operating misting equipment mounted on a roller table.

Table B.6.14.1.1.1-4: Estimation of operator exposures for treatment of seed potatoes using misting equipment mounted over a roller table

TREATMENT RATE				
Application dose	0.25	kg as/tonne		
Seed potatoes planted	2.5	tonne/ha		
Daily seed potato planting rate	3.5	ha/day		
Treatment rate	2.2	kg as/day		
DERMAL EXPOSURE DURING APPLICATION				
Dermal unit exposure (body)	64.4	mg/kg as		
Dermal exposure to as (body)	141.7	mg/day		
Percent absorbed	0.538	%		
Absorbed dose	0.76	mg/day		
	Hands		Hands	
PPE	None		Gloves	
Penetration	100		10	%
Dermal unit exposure (hands)	93.0		93.0	mg/kg as
Dermal exposure to as (hands)	204.6		20.5	mg/day
Percent absorbed	0.538		0.538	%
Absorbed dose	1.1		0.11	mg/day
Total dermal absorbed dose	1.86		0.87	mg/day
INHALED EXPOSURE DURING APPLICATION				
Inhalation unit exposure	0.79	mg/kg as		
Inhalation exposure to as	1.7	mg/day		
Percent absorbed	100	%		
Absorbed dose	1.7	mg/day		
PREDICTED EXPOSURE				
	Dermal Exposure		Inhalation Exposure	
No gloves	346.3		1.7	mg/day
Gloves during spray application & mixing/loading	162.2		1.7	mg/day

A summary of the estimated operator exposures is provided in the following table.

Table B.6.14.1.1.1-5: Estimated operator exposures - Roller table treatment of seed potatoes

Crop & application method	Dermal exposure (mg/person/day)			Inhalation exposure (mg/person/day)
	Body	Hands	Total	
No PPE				
Potatoes (roller table)	141.7	204.6	**346.3**	1.7
With PPE				
Potatoes (roller table)	141.7	20.5	**162.2**	1.7

Comparison of estimated and tolerable exposures

The estimated operator exposures were compared the proposed AOEL (0.16 mg/kg bw/day) (see B.6.10.9). Systemic exposures were estimated assuming a 60 kg body weight, 0.538% absorption of dermal exposures during application (Savides, M.C. 2003 and Ward, R. J. 2003) and 100% absorption of inhalation exposures.

Table B.6.14.1.1.1-6: Estimated operator exposures to tolclofos-methyl as a percentage of the AOEL - Roller table exposure calculations

Crop & application Method	Dermal exposure (mg/kg bw/day)	Inhalation exposure (mg/kg bw/day)	Systemic exposure (mg/kg bw/day)	% AOEL
No PPE				
Potatoes (roller table spray)	5.77	0.028	**0.059**	**37%**
With PPE				
Potatoes (roller table spray)	2.7	0.028	**0.042**	**26%**

Conclusions

Operator exposures were estimated for treatment of seed potatoes using misting equipment mounted over a roller table. The basis for these exposure estimates is an operator exposure study effectuated on the pesticide thiabendazole in which a similar treatment technique was used. The estimated operator exposures were 37% and 26% of the AOEL whitout and with PPE, respectively. These results indicate that tolclofos-methyl can be applied to seed potatoes using misting equipment mounted on a roller table in a manner consistent with label recommendations, without potential risks to operators.

B.6.14.1.1.2 Estimation of operator exposure during treatment of seed potatoes using dusting machines and related activities

Reference	: Stevens, E.R., Davis, J.E., 1981
Title of study	: Evaluation of operator hazards – ULV application of thiabendazole to potatoes on harvesting equipment
Test substance	: 5% Captan Seed Protectant (5% dust formulation of captan)
Guideline	: In-house method
GLP	: No
Acceptability	: Yes

Materials and methods

Operator exposure data for the application of tolclofos-methyl dust formulations to seed potatoes in seed dusting machines and related activities are not available. However, data from an operator exposure study, "Potential Exposure of Workers During Seed Potato Treatment with Captan," can be used to estimate exposures to operators handling dust formulations of tolclofos-methyl in a similar situation.

In this study, workers who performed the following activities were monitored: filling hoppers of seed dusting machines, cutting and sorting potatoes on seed cutting machines located near the dusters, driving tractors and planting the treated seed potatoes, and observing the planting by riding behind the planter. 5% Captan Seed Protectant was applied at a rate of 1.5 lb dust (0.075 lb as) per 100 pounds of potatoes. The application rate corresponds to 0.75 kg as/tonne seed potatoes. The material was dispensed from 50 lb bags.

This study was conducted at two facilities. At the first site, the dusting machine was located outside, and the cutting machine was located inside the building with a plastic sheet in place to protect workers from blowing

dust. Four cutting machine workers were located 1-3 metres from the dusting machine. A conveyor belt, which fed seed potatoes from the cutting machine to the dusting machine, ran through a slot in the plastic sheet. At the second site, the dusting and cutting machines were both located inside, though doors remained open when the wind was not excessive to facilitate changing trucks. Six cutting machine workers were located 1-5 metres from the dusting machine. At both sites, tractor drivers and planter observers were also monitored during planting activities. The driver transferred treated potatoes to the planter hoppers, and the observer assisted in the transfer. Approximately ¾-2 hours was required to prepare a truckload of seed. Application of 2 filling and planting cycles took approximately ¾ hr.

All workers wore head coverings and long-sleeved shirts or jackets. Exposures to the hands, face, and neck, as well as respiratory exposure, were monitored. Cutting machine workers wore rubber gloves, so their hand exposure was not monitored. Dusting machine workers wore canvas-based leather gloves, and their hand exposure was monitored. Hand exposures were measured using an alcohol rinse, and respiratory exposure was measured using modified respirators with gauze-fitted pads. Other dermal exposures were monitored using gauze patches attached outside the clothing to both shoulders and the upper centers of the back and chest. Entire respirator pads and 25 cm^2 portions of the dermal pads were extracted with toluene and dried with anhydrous sodium sulfate. Analysis was accomplished with gas chromatography with electron capture. Mean recovery of fortified pads was 97.7±2.7%.

Findings

Reported average exposure data are summarized in Table B.6.14.1.1.2-1.

Table B.6.14.1.1.2-1: Measured exposures for workers loading dusting machines and performing related activities with seed potatoes treated with Captan seed protection product

Operation	Exposure (mg/h)		
	Dermal (face and neck)	Dermal (hands)	Respiratory
Filling duster located outside (rocky seed)	7.2 ± 2.2 (n=3)	7.6 ± 5.5 (n=3)	1.7 ± 0.6 (n=5)
Filling duster located outside (clean seed)	4.5 ± 0.2 (n=3)	3.0 ± 2.0 (n=3)	0.61 ± 0.23 (n=3)
Filling duster located inside (clean seed)	0.95 ± 0.41 (n=9)	0.093 ± 0.068 (n=7)	0.15 ± 0.12 (n=7)
Cutting (cutter inside, duster outside)	0.70 ± 0.42 (n=12)	n.d.	0.042 ± 0.034 (n=12)
Cutting (cutter inside, duster inside)	0.40 ± 0.41 (n=18)	n.d.	0.037 ± 0.036 (n=18)
Driving tractor pulling planter (includes loading planter)	0.34 ± 0.21 (n=5)	0.033 ± 0.016 (n=5)	0.037 ± 0.020 (n=10)
Observer riding on planter (includes loading planter)	0.31 ± 0.14 (n=5)	0.015 ± 0.012 (n=5)	0.027 ± 0.031 (n=10)

n.d.: no data - Cutters wore rubber gloves so hand exposures were not monitored.

Conclusions Measured dermal and inhalation exposures to Captan seed protection product were observed to depend on the activity performed (e.g., filling, cutting, driving, or observing). All exposures were generally low, though treating rocky potatoes resulted in increased exposure. Isolation of the cutting machine from the dusting machine did not dramatically impact exposures to cutters.

Data used for the calculations

In the original Stevens and Davis (1981) study, dermal exposures to only the head and neck were measured. To estimate potential dermal exposures to the rest of the body, exposure data in the U.S. EPA Pesticide Handlers

Exposure Database (PHED) for mixing/loading wettable powder formulations were evaluated because the wettable powder formulation is most similar to the dust formulation used in the original study. Analysis of mixing/loading PHED exposure data for wettable powder formulations indicates that exposure to the body is approximately equal to that for the head/neck. To compensate for the lack of body exposure data reported in the study, total dermal exposure (except the hands) was estimated by doubling the measured dermal exposures to the head/neck reported in the study. Exposure factors were calculated at the 75th percentile based on the mean and standard deviations reported in Table B.6.14.1.1.2-1 assuming that the underlying data are normally distributed. The resulting exposure factors are summarised in Table B.6.14.1.1.2-2.

Table B.6.14.1.1.2-2: Estimated exposure factors for loading a seed dusting machine and related activities derived from a study of operators applying Captan dust formulations to potatoes

Operation	Exposure (mg/h)			
	Dermal (head and neck)	Dermal (hands)	Dermal [a] (total)	Respiratory
Filling duster located outside (rocky seed)	8.7	11.3	28.7	2.1
Filling duster located outside (clean seed)	4.6	4.3	13.6	0.77
Filling duster located inside (clean seed)	1.2	0.14	2.6	0.23
Cutting (cutter inside, duster outside)	0.98	n.d.	2.0	0.065
Cutting (cutter inside, duster inside)	0.68	n.d.	1.4	0.061
Driving tractor pulling planter (includes loading planter)	0.48	0.044	1.0	0.050
Observer riding on planter (includes loading planter)	0.40	0.023	0.83	0.048

a: *To account for the lack of exposure data for the body, total dermal exposure is estimated as twice the measured head/neck exposure plus the measured hand exposure.*

Using the 75th percentile exposure factors listed Table B.6.14.1.1.2-2, dermal and inhalation exposures to Captan were estimated assuming 6 hours/day of exposure, 60 kg body weight and 0.015% dermal absorption for the concentrate (Savides, M.C. 2003 and Ward, R. J. 2003, point B.6.12.1 and 2). The resulting exposure estimates were then multiplied by a factor of (0.25 kg as/tonne / 0.75 kg as/tonne) to account for the lower application rate of tolclofos-methyl compared to the application rate of Captan in the surrogate study.

As an example calculations of the systemic exposure for operators filling duster located outside (rocky seed) are as follows:

Total dermal exposure 28.7 mg/h x 6h x 0.015% dermal absorption + respiratory exposure 2.1 mg/h = 0.21 mg/kg bw/day. That is multiplied with the factor (0.25 kg as/tonne / 0.75 kg as/tonne) x 0.21 mg/kg bw/day = 0.07 mg/kg bw/day.

Estimated exposures to tolclofos-methyl are summarised below in Table B.6.14.1.1.2-3.

Table B.6.14.1.1.2-3: Estimated exposures to tolclofos-methyl for loading a seed dusting machine and related activities derived from a study of operators applying Captan dust formulations to potatoes

Operation	Captan Exposure			Systemic Exposure to tolclofos-methyl (mg/kg bw/d)
	Total Dermal (mg/h)	Respiratory (mg/h)	Systemic (mg/kg bw/d)	
Operator Activities				
Filling duster located outside (rocky seed)	28.7	2.1	0.21	0.070
Filling duster located outside (clean seed)	13.6	0.77	0.077	0.026
Filling duster located inside (clean seed)	2.6	0.23	0.023	0.0080
Bystander Activities				
Cutting (cutter inside, duster outside)	2.0	0.065	0.0065	0.0022
Cutting (cutter inside, duster inside)	1.4	0.061	0.0061	0.0020
Worker Activities				
Driving tractor pulling planter (includes loading planter)	1.0	0.050	0.0050	0.0017
Observer riding on planter (includes loading planter)	0.83	0.048	0.0048	0.0016

Comparison of estimated and tolerable exposures

On the basis of the operator exposures estimated using the operator exposure study, the portion of the proposed AOEL (0.16 mg/kg bw/day) (see B.6.10.9) accounted for is as shown below. These calculations are summarised in Table B.6.14.1.1.2-4.

Table B.6.14.1.1.2-4: Estimated exposures for operators loading a potato seed dusting machine with tolclofos-methyl and related activities (PPE worn)

Operation	Tolclofos-methyl - Systemic Exposure (mg/kg/d)	% AOEL
Operator Activities		
Filling duster located outside (rocky seed)	0.070	44%
Filling duster located outside (clean seed)	0.026	16%
Filling duster located inside (clean seed)	0.008	5%
Bystander Activities		
Cutting (cutter inside, duster outside)	0.0022	1.4%
Cutting (cutter inside, duster inside)	0.0020	1.2%
Worker Activities		
Driving tractor pulling planter (includes loading planter)	0.0017	1%
Observer riding on planter (includes loading planter)	0.0016	1%

Conclusions and comments

The exposure estimates in Table B.6.14.1.1.2-4 demonstrate that operator, bystander and worker exposures are below the AOEL when PPE is worn. The surrogate study forming the basis of these calculations did not measure exposures when PPE was not worn.

In the study, 75th percentile exposure factors have been used. According to the RMS worst case exposure factors would have been more advisable to use. However, systemic exposures are below the AOEL and the study is considered acceptable.

B.6.14.1.1.3 Estimation of operator exposure during in furrow spraying of potatoes at the time of planting: Estimations using the UK POEM and German models

Tolclofos-methyl 50SC may be applied directly to seed potatoes in-furrow at the time of planting.

The following assumptions have been used in calculating operator exposure:

Crop	Area treated per day	Application rate
Potatoes (field)	3.5 ha/day (maximum practicable planting rate for seed potatoes)	0.25 kg as/tonne of seed potatoes (maximum label rate), planted at a rate of 2.5 tonne/ha = 0.625 kg as/ha

The maximum practicable daily rate for planting potatoes (3.5 ha/day) was obtained from "The Farm Management Handbook" published by the Scottish Agricultural College. The rate of treating seed potatoes with tolclofos methyl is limited by the rate at which they can be planted. Thus, the maximum practicable planting rate determines the rate at which the product will be used to treat seed potatoes prior to planting. Seed potatoes (first earlies) are planted at a rate of 2.5 tonne/ha (J.A.R. Lockhart, A.J.L. Wiseman (1970) Introduction to crop husbandry, Second Edition, Pergamon Press).

Penetration and absorption data

Category of penetration/absorption	Penetration/absorption rate	Remark
Universal protective gloves (plant protection) when handling the undiluted product (Dm)	PPE reduction coefficient = 0.01	General for all formulations
Universal protective gloves (plant protection) during application / handling of the diluted product (Da(h))	PPE reduction coefficient = 0.01	General for all formulations
Standard protective garment (plant protection) and sturdy footwear during application / handling of the diluted product (Da(b))	PPE reduction coefficient = 0.05	General for all formulations
Absorption of inhaled material	100%	In the absence of specific data
Dermal absorption of dermal exposure	0.015% during mixing/loading and 0.538% during spray application	Savides, M.C., 2003 (QM-0057) and Ward, R. J., 2003 (QM-0056)

Estimation of operator exposure during in furrow spraying using the UK POEM model

Mixer/loader exposures were estimated using the UK model for field crop sprayers. Applicator exposures were not estimated because such exposures are negligible for this application method. The estimation of operator exposure was completed for the two situations in which personal protective equipment (PPE) was worn or was not worn.

Table B.6.14.1.1.3-1 UK POEM calculation for potatoes (in-furrow application, mixer/loader exposure only, SC formulation)

PRODUCT DATA				
Product name				
Active ingredient	tolclofos methyl			
Concentration	500	mg/ml		
Formulation type	SC			
EXPOSURE DURING MIXING AND LOADING				
Container size	1	litres		
Hand contamination/operation	0.01	ml		
Application dose	1.25	litres product/ha	2.2	kg as/day
Work rate	3.5	ha/day		
Number of operations	5	/day		
Hand contamination	0.05	ml/day		
Protective clothing	None	Gloves		
Transmission to skin	100	5	%	
Dermal exposure to formulation	0.05	0.0025	ml/day	
Concentration of as	500	500	mg/ml	
Dermal exposure to as	25	1.25	mg/day	
Percent absorbed	0.015	0.015	%	
Absorbed dose	0.00375	0.0001875	mg/day	

PREDICTED EXPOSURE

	Dermal Exposure	Inhalation Exposure	
No gloves	25	n.a.	mg/day
Gloves during mixing/loading	1.25	n.a.	mg/day

Comparison of estimated and tolerable exposures

On the basis of the estimation of operator exposure during in furrow spraying of potatoes using the UK model, the portion of the proposed systemic AOEL (0.16 mg/kg bw/day) (see B.6.10.9) accounted for is shown below. Systemic exposures were estimated assuming a 60 kg body weight, 0.015% absorption of dermal exposures during mixing/loading, Inhalation and application exposures are negligible during in furrow spraying.

Table B.6.14.1.1.3-2: Estimated operator exposures during in furrow application of tolclofos-methyl 50SC to potatoes as a percentage of the AOEL - UK POEM calculations

Crop	Dermal exposure (mg/day)	Dermal exposure (mg/kg bw/day)	Systemic exposure (mg/kg bw/day)	% AOEL
Potatoes (without PPE)	25	0.417	0.000063	**0.04%**
Potatoes (with PPE)	1.25	0.021	0.0000032	**0.002%**

Conclusions

Using the UK model, operator exposures were estimated for in-furrow treatment of seed potatoes. The estimated operator exposures are considerably less than the AOEL whether or not PPE is worn. These results indicate that tolclofos-methyl 50SC formulations can be used in a manner consistent with label recommendations without potential risks to operators.

Estimation of operator exposure during in furrow spraying using the German model

Tolclofos-methyl 50SC may be applied directly to seed potatoes in-furrow at the time of planting. Mixer/loader exposures were estimated using the mixing portion of the German model for application of liquid formulations to

field crops. Applicator exposures were not estimated because such exposures are negligible for this application method.

Table B.6.14.1.1.3-3 German model calculations for potatoes (in-furrow application, mixer/loader exposure only, SC formulation)

Amount handled per day = treated area × use rate = 3.5 ha/day × 0.625 kg as/ha = 2.1875 kg as/day

No PPE

I_m	=	0.0006	mg/kg as ×	2.1875	kg as/day		=	0.0013125	mg/person/day
D_m	=	2.4	mg/kg as ×	2.1875	kg as/day		=	5.25	mg/person/day

With PPE

I_m	=	0.0006	mg/kg as ×	2.1875	kg as/day		=	0.0013125	mg/person/day
D_m	=	2.4	mg/kg as ×	2.1875	kg as/day	× 0.01*	=	0.0525	mg/person/day

Abbreviations: I = estimated inhalation exposure m = during mixing/loading
D = estimated dermal exposure
* PPE reduction coefficient

Comparison of estimated and tolerable exposures

On the basis of the operator exposures estimated using the German model, the portion of the proposed systemic AOEL (0.16 mg/kg bw/day, see B.6.10.9) accounted for is shown below. Systemic exposures were estimated assuming a 60 kg body weight, 0.015% absorption of dermal exposures during mixing/loading, and 100% absorption of inhalation exposures.

Table B.6.14.1.1.3-4: Estimated operator exposures during in furrow application of tolclofos-methyl 50SC to potatoes as a percentage of the AOEL – German model calculations

Crop	Dermal exposure (mg/day)	Inhalation exposure (mg/day)	Dermal exposure (mg/kg bw/day)	Inhalation exposure (mg/kgbw/day)	Systemic exposure (mg/kg bw/day)	% AOEL
Potatoes (without PPE)	5.25	0.0013	0.088	0.000022	0.000035	**0.02%**
Potatoes (with PPE)	0.0525	0.0013	0.00088	0.000022	0.000022	**0.014%**

Conclusions

Using the German model, operator exposures were estimated for applications of tolclofos-methyl 50SC and 50WP formulations arising from in-furrow treatment of seed potatoes. The estimated operator exposures are considerably less than the AOEL whether PPE is worn or not. These results indicate that tolclofos-methyl 50SC can be used in a manner consistent with label recommendations without potential risks to operators.

B.6.14.1.1.4 Measurement of operator exposure during potato seed treatment with dust formulation

Reference	: Jackson, C. M., 1995a; Jackson, C. M., 1995b; Burden, A.N., 1995; Jackson, C. M., 1995c
Title of study	: Tolclofos methyl dust 10% (Code: CR 17495) Rizolex: Potato treatment operator exposure study; 1st amendment to report No TOX/94/192-61 Rizolex dust 10% Code: CR 17495 potato treatment operator exposure study; 1st addendum to report S-3349/T77 tolclofos methyl dust 10% (Code: CR 17495) Rizolex: Potato treatment operator exposure study, analytical phase; 1st amendment to addendum to report No TOX/94/192-61 (study No TOX93301) Rizolex dust 10% Code: CR 17495 operator exposure study, analytical phase
Test substance	: "Storite" (45% thiabendazole)
Guideline	: In-house method
GLP	: No
Acceptability	: Yes

Worst-case exposures for applications of tolclofos-methyl to seed potatoes are represented by the 10% dust formulation. Exposure may occur during mixing/loading of the seed potatoes, which are mixed with the dust formulation in the hopper of the planter. An operator exposure study was conducted which measured operator exposures during hopper loading with dust formulation and potatoes and planting of the crop by driving the planter loaded with treated potatoes.

Materials and methods

Rizolex (dust formulation containing 10.3% w/w tolclofos-methyl) was utilised in an operator exposure field trial to measure operator exposure resulting from application of Rizolex to seed potatoes at the time of planting. The field trial phase of this study occurred between 15 April and 11 May, 1994. The study was conducted at eight sites. At two of the sites, separate subjects conducted the loading and application tasks, while at the remaining six sites, a single subject completed both loading and application tasks. Typically, subjects filled the planter's hopper half full with seed potatoes, sprinkled half of the required quantity of Rizolex over the potatoes, and repeated the process with the remaining seed potatoes and Rizolex. On average, subjects treated 7.8 tonnes of potatoes with 19.7 kg of Rizolex during a mean trial period of 414 minutes (6.9 hr). The average application rate of Rizolex was 253 g as/tonne.

Study subjects wore the label-required personal protective clothing (coveralls), gloves, and respiratory equipment when loading the hopper and handling contaminated surfaces. Potential dermal exposures were assessed by sampling and analysing outer and inner clothing.

Outer clothing consisted of a polyester cotton coverall, disposable nitrile gloves, a dust mask and a cotton cap. Inner clothing consisted of a cotton T-shirt, cotton long pants, cotton gloves and a cotton balaclava tucked

beneath the top of the coverall. Samples from the inner clothing and the cap were considered to represent potential dermal exposures to the skin and scalp. Hand exposures were measured by separately analysing the outer nitrile gloves and inner cotton gloves.

Potential inhalation exposures were assessed using sampling pumps located in the breathing zone. Therefore, potential inhalation exposures are not representative of likely inhalation exposure because proper respiratory protection equipment must be worn.

Samples were analysed by gas chromatography with nitrogen/phosphorus detection following extraction with hexane or acetone. Procedural recovery tests performed in parallel with laboratory analysis of each batch of exposure samples yielded a mean recovery of 100% across all substrates. Overall mean recovery efficiencies from field fortified samples ranged from 68 to 114%. Storage stability tests demonstrated 98 and 96% recovery efficiencies of hexane extraction following 28 days freezer storage of cotton long sleeved vests and balaclavas, respectively, to which 100 mg Rizolex has been added.

Tolclofos-methyl residues detected on glass fibre filters (i.e., inhalation samples) ranged from <0.02 to 0.51 mg per working period. Tolclofos-methyl residues on operator clothing ranged from <0.10 to 23.6 mg on inner garments and from <0.10 to 128 on outer garments.

Testing facility was [redacted] (field phase) and [redacted] (analytical phase).

Findings

Potential dermal exposures assessed from inner clothing and cap samples and potential inhalation exposures are summarised in the tables below.

Table B.6.14.1.1.4-1: Dermal exposures to tolclofos-methyl assessed using outer clothing and cap

Activity	Trial site/operator ref.	mg/kg bw/day	mg/kg a.s.
Treatment	Site 1/Loader	3.01	15.30
	Site 3/Loader	4.51	14.02
Planting	Site 1/Driver	0.521	2.96
	Site 3/Driver	0.427	1.61
Treatment and planting	Site 2	2.79	10.25
	Site 4	1.58	5.82
	Site 5	2.21	9.19
	Site 6	1.03	7.83
	Site 7	3.47	10.05
	Site 8	1.10	6.01
	Mean	2.03	8.19
	SD	0.97	1.96
Overall	Mean	2.06	8.30
	SD	1.36	4.40

Table B.6.14.1.1.4-2: Potential dermal exposures to tolclofos-methyl assessed using inner clothing and cap

Activity	Trial site/operator ref.	mg/kg bw/day	mg/kg a.s.
Treatment	Site 1/Loader	0.544	2.77
	Site 3/Loader	1.019	3.17
Planting	Site 1/Driver	0.277	1.57
	Site 3/Driver	0.079	0.30
Treatment and planting	Site 2	0.890	3.28
	Site 4	0.287	1.06
	Site 5	0.469	1.95
	Site 6	0.228	1.74
	Site 7	0.456	1.32
	Site 8	0.220	1.21
	Mean	0.425	1.76
	SD	0.253	0.82
Overall	Mean	0.447	1.84
	SD	0.302	0.97

Table B.6.14.1.1.4-3: Potential inhalation exposures to tolclofos-methyl

Activity	Trial site/operator ref.	mg/kg bw/day
Treatment	Site 1/Loader	0.025
	Site 3/Loader	0.106
Planting	Site 1/Driver	0.004
	Site 3/Driver	0.005
Treatment and planting	Site 2	0.042
	Site 4	0.011
	Site 5	0.006
	Site 6	0.009
	Site 7	0.022
	Site 8	0.020
	Mean	0.018
	SD	0.013
Overall	Mean	0.025
	SD	0.031

The overall mean potential dermal exposure was measured to be 0.447 mg/kg bw/day (Table B.6.14.1.1.4-2). The overall mean potential inhalation exposure was measured to be 0.025 mg/kg bw/day (Table B.6.14.1.1.4-3). Comparison of dermal exposures assessed using outer clothing and inner clothing samples demonstrated that wearing coveralls provided a mean protection factor of 82 percent (i.e., inner clothing exposures were 18 percent of the outer clothing exposures).

Comparison of estimated and tolerable exposures

From the study results, average dermal exposures were estimated to be 0.447 mg/kg bw/day, based on inner clothing samples (Table B.6.14.1.1.4-2). Because the dermal exposures associated with loading and driving phases were not clearly separated, 0.538% absorption of dermal exposures (B.6.12.1 and 2) was assumed as a worst case. When adjusted for 0.538% absorption, average absorbed dermal exposures were estimated to be 0.002 mg/kg bw/day, The average potential inhalation exposures, which were monitored through personal air samplers, were estimated to be 0.025 mg/kg bw/day (Table B.6.14.1.1.4-3). The estimated average estimates of total exposure are thus 0.027 mg/kg bw/day. These exposures are 17% of the AOEL of 0.16 mg/kg bw/day (see B.6.10.9), indicating that dust formulations of tolclofos-methyl can be safely applied to potatoes if label directions are followed. These exposure estimates apply to the total exposure associated with the loading and driving phases. Exposure values are well below the AOEL even when assuming a worst case and thus using the

dermal exposure value obtained for site 3/loader during treatment: 1.019 mg/kg bw/day x 0.538% dermal absorption and adding the average inhalation exposure of 0.025 mg/kg bw/day = 0.03 mg/kg bw/day = 19% of AOEL. The average inhalation exposure value is used to obtain a fair view of the extent of inhalation exposure. Even if the inhalation exposure value for site 3/loader, 0.106 mg/kg bw/day would have been used, the AOEL would not be exceeded (exposure is then 70% of AOEL). The relatively high dermal and inhalation exposures for the loader at Site 3 were attributed to her standing downwind while loading the Rizolex into the hopper. Furthermore, actual inhalation exposures are likely to be lower due to the label requirement to wear respiratory protection.

On the basis of the estimated exposures, the portion of the proposed AOEL (0.16 mg/kg bw/day, see B.6.10.9) accounted for is shown in the following table. Systemic exposures were estimated assuming as a worst-case 0.538% dermal absorption and 100% inhalation absorption.

Crop	Total Systemic Exposure – 60 kg per person (mg/kg bw/day)		% of AOEL	
	no PPE	with PPE	no PPE	with PPE
Potatoes	n.a. *	0.027	n.a. *	17%

**Data from the operator exposure study were available for operators wearing label-required PPE only, although inhalation exposures are based on personal air samplers.*

Conclusions When applied as directed, average potential operator exposure associated with treating seed potatoes with Rizolex (dust formulation containing 10% w/w tolclofos-methyl) was found to be 0.447 mg/kg bw/day for dermal exposure and 0.025 mg/kg bw/day for inhalation exposure. The estimated operator exposures are less than the AOEL. These results indicate that tolclofos-methyl 50SC can be used in a manner consistent with label recommendations without potential risks to operators.

B.6.14.1.2 Lettuce

B.6.14.1.2.1 Estimation of operator exposure during treatment of lettuce using the UK POEM and German models

For lettuce grown in glasshouses, tolclofos-methyl 50WP is applied to and then incorporated into the soil prior to sowing or transplantation. In glasshouses, tolclofos-methyl 50WP is applied using hand-held sprayers and automatic spray equipment.

The application equipment used to apply tolclofos-methyl 50WP is identified below.

Crop	Application equipment
Lettuce (glasshouse)	Automatic spray equipment Hand-held sprayer

The following assumptions have been used in calculating operator exposure:

Crop	Area treated per day	Application rate
Lettuce (glasshouse)	2 ha/day for automatic equipment (based on registrant experience with glasshouse application on lettuce) 1 ha/day for hand-held equipment (default)	2 kg as/ha for lettuce (maximum label rate)

Penetration and absorption data

Category of penetration/absorption	Penetration/absorption rate	Remark
Universal protective gloves (plant protection) when handling the undiluted product (Dm)	PPE reduction coefficient = 0.01	General for all formulations
Universal protective gloves (plant protection) during application / handling of the diluted product (Da(h))	PPE reduction coefficient = 0.01	General for all formulations
Standard protective garment (plant protection) and sturdy footwear during application / handling of the diluted product (Da(b))	PPE reduction coefficient = 0.05	General for all formulations
Absorption of inhaled material	100%	In the absence of specific data
Dermal absorption of dermal exposure	0.015% during mixing/loading and 0.538% during spray application	Savides, M.C., 2003 (QM-0057) and Ward, R. J., 2003 (QM-0056)

Estimation of operator exposure during treatment of lettuce using the UK POEM model

Applications to lettuce in glasshouses may be made with either automatic spray equipment or hand-held sprayers. Tolclofos-methyl 50WP is applied in a soil drench at dilution rates ranging from 1,000 to 2,500 l/ha. Following application, tolclofos-methyl 50WP is incorporated into the soil. When tolclofos-methyl 50WP is applied using automatic equipment, application exposures are negligible, and potential operator exposures are limited to mixing and loading. Potential mixing/loading exposures associated with automatic spray equipment were estimated using the mixing portion of the UK model for field crop sprayers because this model represents the best estimate for exposures associated with mixing in large tanks. Potential exposures associated with hand-held spray application were estimated using the UK model for knapsack sprayers. The estimation of operator exposure was completed for the two situations in which personal protective equipment (PPE) was worn or was not worn.

Table B.6.14.1.2.1-1 UK POEM calculation for lettuce (mixing/loading prior to application by automatic equipment in glasshouses, WP formulation)

PRODUCT DATA			
Product name			
Active ingredient	Tolclofos-methyl		
Concentration	500	mg/g	
Formulation type	WP		
Dose	4	kg product/ha	
Application volume	1000	l/ha	
Work rate/day	2	ha	
DERMAL EXPOSURE DURING MIXING AND LOADING			
Hand contamination/kg a.s.	13.6	mg/kg as	
Hand contamination/day	54.4	mg/day	
Protective clothing	None	Gloves	
Transmission to skin	100	1	%
Dermal exposure to a.s.	54.4	0.544	mg/day
Percent absorbed	0.015	0.015	%
Absorbed dose	0.00816	0.0000816	mg/day
INHALATION EXPOSURE DURING MIXING AND LOADING			
Inhalation exposure/kg a.s.	0.659	mg/kg as	
Inhalation exposure/day	2.636	mg/day	
RPE	none		
Transmission through RPE	100	%	
Inhalation exposure to a.s.	2.636	mg/day	

PREDICTED EXPOSURE

	Dermal Exposure	Inhalation Exposure	
No gloves, No RPE	54.4	2.636	mg/day
Gloves during mixing/loading, No RPE	0.544	2.636	mg/day

Table B.6.14.1.2.1-2 UK POEM calculation for lettuce (knapsack sprayer model, WP formulation)

PRODUCT DATA

Product name			
Active ingredient	Tolclofos-methyl		
Concentration	500	mg/g	
Formulation type	WP		
Dose	4	kg product/ha	
Application volume	1000	l/ha	
Work rate/day	0.4	ha	

EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	171.4	mg/kg as		Extrapolated value from WG data
Hand contamination/day	137.12	mg/day		
Protective clothing	None		Gloves	
Transmission to skin	100		1	%
Dermal exposure to a.s.	137.12		1.3712	mg/day
Percent absorbed	0.015		0.015	%
Absorbed dose	0.020568		0.00020568	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	1.534	mg/kg as
Inhalation exposure/day	1.2272	mg/day
RPE	None	
Transmission through RPE	100	%
Inhalation exposure to a.s.	1.2272	mg/day

EXPOSURE DURING SPRAY APPLICATION

Application technique – Hand-held sprayer (15 l tank): hydraulic nozzles, Outdoor, low level target

Application volume	1000	Litres spray/ha			
Volume of surface contamination	50	ml/h			
Distribution	Hands	Hands	Trunk	Legs	
	25	25	25	50	%
Clothing	none	gloves	permeable	permeable	
Penetration	100	10	20	18	%
Dermal exposure	10	1.25	2.5	4.5	ml/h
Duration of exposure	6	h			

PPE	None	Gloves	
Total dermal exposure to spray	102	49.5	ml/day
Concentration of as	2	2	mg/ml
Dermal exposure to as	204	99	mg/day
Percent absorbed	0.538	0.538	%
Absorbed dose	1.09752	0.53262	mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure to spray	0.02	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	2	mg/ml
Inhalation exposure to a.s.	0.24	mg/day
Percent absorbed	100	%
Absorbed dose	0.24	mg/day

PREDICTED EXPOSURE

	Dermal Exposure	Inhalation Exposure	
No gloves	341.12	1.4672	mg/day
Gloves during spray application & mixing/loading	100.3712	1.4672	mg/day

Table B.6.14.1.2.1-3: Summary of estimated operator exposures during treatment of lettuce - UK model

Crop & application method	Dermal exposure (mg/person/day)			Inhalation exposure (mg/person/day)		
	Mix/load	Spray	Total	Mix/load	Spray	Total
No PPE						
Lettuce (automatic sprayer, WP)	54.4	n.a.	**54.4**	2.64	n.a.	**2.64**
Lettuce (hand-held, WP)	137	204	**341**	1.23	0.24	**1.47**
With PPE						
Lettuce (automatic sprayer, WP)	0.54	n.a.	**0.54**	2.64	n.a.	**2.64**
Lettuce (hand-held, WP)	1.37	99	**100.37**	1.23	0.24	**1.47**

n.a.: not applicable - application and inhalation exposures are negligible for this method of application

Comparison of estimated and tolerable exposures

On the basis of the operator exposures estimated using the UK model, the portion of the proposed AOEL (0.16 mg/kg bw/day, see B.6.10.9) accounted for is shown below. Systemic exposures were estimated assuming a 60 kg body weight, 0.015% absorption of dermal exposures during mixing/loading, 0.538% absorption of dermal exposures during spray application (where applicable) and 100% absorption of inhalation exposures.

Table B.6.14.1.2.1-4: Estimated operator exposures to tolclofos-methyl 50WP during treatment of lettuce as % of the AOEL - UK POEM calculations

Crop & application method	Dermal exposure (mg/kg bw/day)		Inhalation exposure (mg/kg bw/day)	Systemic exposure (mg/kg bw/day)	% AOEL
	Mix/load	Spray			
No PPE					
Lettuce (automatic sprayer, WP)	0.91	n.a.	0.044	**0.044**	**28%**
Lettuce (hand-held, WP)	2.29	3.4	0.024	**0.043**	**27%**
With PPE					
Lettuce (automatic sprayer, WP)	0.009	n.a.	0.044	**0.044**	**28%**
Lettuce (hand-held, WP)	0.023	1.65	0.024	**0.033**	**21%**

Conclusions

Using the UK model, operator exposures were estimated for greenhouse applications to lettuce using automatic spray equipment and hand-held sprayers. The estimated operator exposures are less than the AOEL whether or not PPE is worn. These results indicate that tolclofos-methyl 50SC and 50WP formulations can be used in a manner consistent with label recommendations without potential risks to operators.

Estimation of operator exposure during treatment of lettuce using the German model

Applications of tolclofos-methyl 50WP to lettuce in glasshouses may be made with either automatic spray equipment or hand-held sprayers. Tolclofos-methyl 50WP is applied in a soil drench at dilution rates ranging from 1,000 to 2,500 liters/ha. Following application, tolclofos-methyl 50WP is incorporated into the soil. When tolclofos-methyl 50WP is applied using automatic equipment, application exposures are negligible, and potential operator exposures are limited to mixing and loading. Potential mixing/loading exposures associated with automatic spray equipment were estimated using the mixing portion of the German model for field crops because this model represents the best estimate for exposures associated with mixing in large tanks. Potential exposures associated with hand-held spray application were estimated using the German model for hand-held equipment.

Table B.6.14.1.2.1-5 German model calculations for lettuce (automatic spray equipment, mix/load exposures only, WP formulation)

Amount handled per day = treated area × use rate = 2 ha/day × 2 kg as/ha = 4 kg as/day

No PPE

I_m	=	0.07	mg/kg as ×	4	kg as/day		=	0.28	mg/person/day
D_m	=	6.0	mg/kg as ×	4	kg as/day		=	24	mg/person/day

With PPE

I_m	=	0.07	mg/kg as ×	4	kg as/day		=	0.28	mg/person/day
D_m	=	6.0	mg/kg as ×	4	kg as/day	× 0.01*	=	0.24	mg/person/day

Abbreviations: I = estimated inhalation exposure m = during mixing/loading
D = estimated dermal exposure
* PPE reduction coefficient

Table B.6.14.1.2.1-6 German model calculations for lettuce (hand-held sprayer in glasshouse, WP formulation)

Amount handled per day = treated area × use rate = 1 ha/day × 2 kg as/ha = 2 kg as/day

No PPE

I_m	=	0.8	mg/kg as ×	2	kg as/day		=	1.6	mg/person/day
D_m	=	50	mg/kg as ×	2	kg as/day		=	100	mg/person/day
I_a	=	0.3	mg/kg as ×	2	kg as/day		=	0.6	mg/person/day
$D_{a(c)}$	=	4.8	mg/kg as ×	2	kg as/day		=	9.6	mg/person/day
$D_{a(h)}$	=	10.6	mg/kg as ×	2	kg as/day		=	21.2	mg/person/day
$D_{a(b)}$	=	25	mg/kg as ×	2	kg as/day		=	50	mg/person/day

Abbreviations: I = estimated inhalation exposure m = during mixing/loading; a = during application
D = estimated dermal exposure (c) = head; (h) = hands; (b) = body

With PPE

I_m	=	0.8	mg/kg as ×	2	kg as/day		=	1.6	mg/person/day
D_m	=	50	mg/kg as ×	2	kg as/day	× 0.01*	=	1	mg/person/day
I_a	=	0.3	mg/kg as ×	2	kg as/day		=	0.6	mg/person/day
$D_{a(c)}$	=	4.8	mg/kg as ×	2	kg as/day		=	9.6	mg/person/day
$D_{a(h)}$	=	10.6	mg/kg as ×	2	kg as/day	× 0.01*	=	0.212	mg/person/day
$D_{a(b)}$	=	25	mg/kg as ×	2	kg as/day	× 0.05*	=	2.5	mg/person/day

Abbreviations: I = estimated inhalation exposure m = during mixing/loading; a = during application
D = estimated dermal exposure (c) = head; (h) = hands; (b) = body
* PPE reduction coefficient

Table B.6.14.1.2.1-7: Estimated operator exposures during treatment of lettuce- German model

Crop & application method	Dermal exposure (mg/person/day)			Inhalation exposure (mg/person/day)		
	Mix/load	Spray	Total	Mix/load	Spray	Total
No PPE						
Lettuce (automatic sprayer, WP)	24	n.a.	**24**	0.28	n.a.	**0.28**
Lettuce (hand-held, WP)	100	80.8	**180.8**	1.6	0.6	**2.2**
With PPE						
Lettuce (automatic sprayer, WP)	0.24	n.a.	**0.24**	0.28	n.a.	**0.28**
Lettuce (hand-held, WP)	1	12.312	**13.312**	1.6	0.6	**2.2**

n.a.: not applicable - application exposures are negligible for this method of application

Comparison of estimated and tolerable exposures

On the basis of the operator exposures estimated using the German model, the portion of the proposed AOEL (0.16 mg/kg bw/day, see B.6.10.9) accounted for is shown below. Systemic exposures were estimated assuming

a 60 kg body weight, 0.015% absorption of dermal exposures during mixing/loading, 0.538% absorption of dermal exposures during spray application (where applicable) and 100% absorption of inhalation exposures.

Table B.6.14.1.2.1-8: Estimated operator exposures to tolclofos-methyl 50WP duringtreatment of lettuce as % of the AOEL - German model calculations

Crop & application method	Dermal exposure (mg/kg bw/day)		Inhalation exposure (mg/kg bw/day)	Systemic exposure (mg/kg bw/day)	% AOEL
	Mix/load	Spray			
No PPE					
Lettuce (automatic sprayer, WP)	0.34	n.a.	0.0040	**0.004**	**2.5 %**
Lettuce (hand-held, WP)	1.43	1.15	0.031	**0.038**	**24 %**
With PPE					
Lettuce (automatic sprayer, WP)	0.0034	n.a.	0.0040	**0.004**	**2.5 %**
Lettuce (hand-held, WP)	0.0143	0.176	0.031	**0.032**	**20 %**

Conclusions

Using the German model, estimations were made of operator exposures of tolclofos-methyl 50WP formulations arising during greenhouse applications to lettuce using automatic spray equipment and hand-held sprayers. The estimated operator exposures are considerably less than the AOEL whether PPE is worn or not. These results indicate that tolclofos-methyl 50WP can be used in a manner consistent with label recommendations without potential risks to operators.

B.6.14.2 Summary of operator exposure

Operator exposures to tolclofos-methyl (WP/SC formulation containing 50% tolclofos-methyl or dust formulation containing 10% tolclofos-methyl) were estimated or measured.

Potatoes: Estimations of operator exposure to tolclofos-methyl 50SC during treatment of seed potatoes in-furrow at the time of planting were predicted using the UK POEM and German models.

Tolclofos-methyl 50SC may also be applied to seed potatoes prior to planting with misting equipment in which hydraulic nozzles have been mounted on a roller table. Operator exposures were estimated based on a surrogate study for similar roller table spray applications to seed potatoes.

10% dust formulation of tolclofos-methyl may also be added to potatoes in the hoppers of planters. Operator exposures for this method of application have been measured. The dust formulation may also be added to potatoes in seed dusting machines, resulting in exposures to operators filling the hoppers of the seed dusting machines, cutting and sorting potatoes near the dusting machines and driving/riding planters loaded with treated potatoes. Operator exposures for seed dusting machines and related activities were estimated based on data from a surrogate study involving treatment with a different product.

Lettuce: Estimations of operator exposures to tolclofos-methyl 50WP during treatment of lettuce in glasshouses made with either automatic spray equipment or hand-held sprayers were predicted using the UK POEM and German models.

Table B.6.14.2-1 Summary of estimated/measured exposures to tolclofos-metyl

Type of study/estimation	Operator/ bystander/ worker	Crop/application method	Result (% of AOEL)		Section in DAR
			+ PPE	– PPE	
UK POEM	Operator	Potatoes (in-furrow spray, SC)	0.002 %	0.04 %	B.6.14.1.1.3
		Lettuce (automatic sprayer, WP)	28 %	27 %	B.6.14.1.2.1
		Lettuce (hand-held sprayer, WP)	21 %	27 %	B.6.14.1.2.1
German model	Operator	Potatoes (in-furrow spray, SC)	0.014 %	0.02 %	B.6.14.1.1.3
		Lettuce (automatic sprayer, WP)	2.5 %	2.5 %	B.6.14.1.2.1
		Lettuce (hand-held sprayer, WP)	20 %	24 %	B.6.14.1.2.1
Tolclofos-methyl dust study	Operator	Potatoes, loading dust in planter hopper with seed potatoes	17 %	Data not available	B.6.14.1.1.4
Thiabendazole roller table study	Operator	Potatoes, treating on misting roller table	26 %	37 %	B.6.14.1.1.1
Captan dust machine loading study	Operator	Potatoes, treating in dusting machinery, and associated tasks	5 - 44 %	Data not available	B.6.14.1.1.2
	Bystander	Potatoes, treating in dusting machinery, and associated tasks	1.2 - 1.4 %	Data not available	
	Worker	Potatoes, treating in dusting machinery, and associated tasks	1 %	Data not available	

Estimated operator, bystander and worker exposures are below the AOEL whether PPE is worn or not worn. The results of these exposure analyses demonstrate that tolclofos-methyl formulations may be safely applied to potatoes and lettuce according to the registered GAP.

B.6.14.3 Bystander exposure

Estimation of bystander exposure assuming personal protective equipment is not used

Operator exposures have been estimated/measured to be less than the AOEL (Table B.6.14.2-1). It is most likely that bystanders would be exposed to a much lower extent than the operator. Bystander exposure has not been measured because no appreciable exposure is anticipated for most methods of application to lettuce and potatoes.

Measurement of bystander exposure

In the case of treating seed potatoes with dust formulations, where bystander exposure might be expected, data from an operator exposure study demonstrate that persons working at cutting tables in the vicinity of the dusting machinery or riding planters stocked with treated seed potatoes experienced exposures of 1.4 % of the AOEL (Table B.6.14.2-1).

B.6.14.4 Worker exposure

Estimation of worker exposure

The methods of applying tolclofos-methyl 50WP preclude subsequent worker exposure. Tolclofos-methyl 50WP is applied to soil in which lettuce will be sown in glasshouses and is then immediately incorporated into the soil. Tolclofos-methyl 50SC is applied in-furrow to seed potatoes at the time of planting, or it may also be applied to seed potatoes using misting equipment on roller tables. These application methods do not result in pesticide residues on foliage. Therefore, it is not necessary to estimate re-entry exposures for workers contacting foliage.

Tolclofos-methyl dust formulations are always applied to seed potatoes in the hopper or in dusting machinery. The product is not applied to potatoes that are subsequently stored, which would result in potential exposures to workers transferring treated seed potatoes from storage to planters. In addition, data from an operator exposure study demonstrate that workers who loaded potatoes from dusting machinery into a planter and subsequently drove the planter or who assisted in loading potatoes and then rode the planter as an observer, experienced exposures that were not greater than 1 % of the AOEL (Table B.6.14.2-1).

It is not necessary to perform additional studies to measure re-entry exposures to workers.

B.6.15 References relied on

Annex No., Reference No.	Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	EU Data Protection Claimed (Y/N)	Owner
IIA, 5.1/01	Mihara, K., Ohkawa, H., Miyamoto, J.	1980	Metabolism of tolclofos-methyl in rats and mice Sumitomo Chemical Co., Ltd. Report No. QM-00-0008 Not GLP, Unpublished	N	SUM
IIA, 5.1/02	Krautter, G.R., Downs, J., Hoglan, N., Marsh, J.D., Lawrence, L.J.	1988a	Metabolism of tolclofos-methyl in the rat Sumitomo Chemical Co., Ltd. Report No. QM-81-0025 GLP, Unpublished	N	SUM
IIA, 5.1/03	Krautter, G.R., Downs, J., Hoglan, N., Marsh, J.D., Lawrence, L.J.	1988b	Final report amendment: Metabolism of tolclofos-methyl in the rat Sumitomo Chemical Co., Ltd. Report No. QM-81-0026 Not GLP, Unpublished	N	SUM

Annex No., Reference No.	Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	EU Data Protection Claimed (Y/N)	Owner
IIA, 5.1/04	Esumi, Y.	1989	Study on metabolism of tolclofos-methyl in rats Sumitomo Chemical Co., Ltd. Report No. QM-91-0035 Not GLP, Unpublished	N	SUM
IIA, 5.1/05	Yu, C.C., Guirguis, A.S.	1987a	Metabolism of ^{14}C tolclofos-methyl in laying hens [redacted] Report No. 8 Sumitomo Chemical Co., Ltd. Report No. QM-71-0028 GLP, Unpublished	N	SUM
IIA, 5.1/06	Yu, C.C.	1987b	Metabolism of ^{14}C tolclofos-methyl in a lactating goat [redacted] Report No. 9 Sumitomo Chemical Co., Ltd. Report No. QM-71-0027 GLP, Unpublished	N	SUM
IIA, 5.2.1/01	Segawa, T.	1978	Acute toxicity of S-3349 in rats and mice Sumitomo Chemical Co., Ltd. Report No. QT-71-0003 Not GLP, Unpublished	N	SUM
IIA, 5.2.1/02	Kynoch, S.R.	1985a	Acute oral toxicity to rats of Rizolex technical [redacted] Report No. Not allocated Sumitomo Chemical Co., Ltd. Report No. QT-51-0083 GLP, Unpublished	Y*	SUM
IIA, 5.2.1/03	Parcell, B.I., Crook, D., Gibson, W.A.	1994	Tolclofos-methyl technical, Code CR21214, rat acute oral toxicity study with cholinesterase estimations AgrEvo Crop Protection Ltd. Report No. TOX93300 Sumitomo Chemical Co., Ltd. Report No. QT-41-0148 GLP, Unpublished	N	AVS
IIA, 5.2.1/04	Pence, D.H.	1978	Acute oral toxicity study in male and female dogs - S-3349 Sumitomo Chemical Co., Ltd. Report No. QT-81-0009 Not GLP, Unpublished	N	SUM
IIA, 5.2.1/01	Segawa, T.	1978	Acute toxicity of S-3349 in rats and mice Sumitomo Chemical Co., Ltd. Report No. QT-71-0003 Not GLP, Unpublished ⇒ Annex IIA, 5.2.1/01	N	SUM

Annex No., Reference No.	Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	EU Data Protection Claimed (Y/N)	Owner
IIA, 5.2.2/02	Kynoch, S.R., Parcell, B.I.	1985b	Acute dermal toxicity to rabbits of Rizolex technical [redacted] Report No. Not allocated Sumitomo Chemical Co., Ltd. Report No. QT-51-0098 GLP, Unpublished	Y*	SUM
IIA, 5.2.3/01	Hardy, C.J., Jackson, G.C., Lewis, D.J., Gopinath, C.	1986	Technical Rizolex - Acute inhalation toxicity in rats - 4-hour exposure [redacted] Report No. Not allocated Sumitomo Chemical Co., Ltd. Report No. QT-61-0133 GLP, Unpublished	N	SUM
IIA, 5.2.4/01	Matsubara, T., Hara, S., Kadota, T.	1978	Eye and skin irritation test of S-3349 in rabbits Sumitomo Chemical Co., Ltd. Report No. QT-80-0002 Not GLP, Unpublished	N	SUM
IIA, 5.2.4/02	Liggett, M.P., Parcell, B.I.	1985a	Irritation effects on rabbit skin of Technical Rizolex [redacted] Report No. Not allocated Sumitomo Chemical Co., Ltd. Report No. QT-51-0091 GLP, Unpublished	Y*	SUM
IIA, 5.2.5/01	Matsubara, T., Hara, S., Kadota, T.	1978	Eye and skin irritation test of S-3349 in rabbits Sumitomo Chemical Co., Ltd. Report No. QT-80-0002 Not GLP, Unpublished ⇒ Annex IIA, 5.2.4/01	N	SUM
IIA, 5.2.5/02	Liggett, M.P., Parcell, B.I.	1985b	Irritation effects on rabbit eye of Technical Rizolex [redacted] Report No. Not allocated Sumitomo Chemical Co., Ltd. Report No. QT-51-0087 GLP, Unpublished	Y*	SUM
IIA, 5.2.6/01	Seaber, J.A.	1985	Delayed contact hypersensitivity in the guinea-pig with technical Rizolex [redacted] Report No. Not allocated Sumitomo Chemical Co., Ltd. Report No. QT-51-0086 GLP, Unpublished	Y*	SUM

Annex No., Reference No.	Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	EU Data Protection Claimed (Y/N)	Owner
IIA, 5.2.6/02	Nakamura, Y.	2001	Skin sensitization test of tolclofos-methyl in guinea-pigs (Maximization test) Sumitomo Chemical Co., Ltd. Report No. QT-0160 GLP, Unpublished	Y*	SUM
IIA, 5.3.1/01	Colley, J., Welch, P.J., Heywood, R., Prentice, D.E., Cherry, C.P., Mullins, P.A., Gibson, W.A. Almond, R.H.	1982	S-3349 toxicity to rats by dietary administration for 4 weeks Sumitomo Chemical Co., Ltd. Report No. QT-21-0049 GLP, Unpublished	N	SUM
IIA, 5.3.2/01	Kimura, J.	1990	90-day oral toxicity study of S-3349 in rats Sumitomo Chemical Co., Ltd. Report No. QT-00-0136 GLP, Unpublished	N	SUM
IIA, 5.3.2/02	Hiromori, T., Suzuki, T., Okuno, Y., Ito, S., Murakami, M., Kadota, T.	1978	Six-month oral toxicity study of S-3349 in rats Sumitomo Chemical Co., Ltd. Report No. QT-80-0004 Not GLP, Unpublished	N	SUM
IIA, 5.3.2/03	Takatsuka, M.	1985a	Quality Assurance Statement: Six-month oral toxicity study of S-3349 in rats Sumitomo Chemical Co., Ltd. Report No. QT-50-0094 Not GLP, Unpublished	N	SUM
IIA, 5.3.2/04	Pence, D.H., Weatherholtz, W.M., Kundzins, W., Alsaker, R.D., Brown, H.R., Greenspun, K.S.	1979b	Subacute dietary administration in dogs - S-3349 Sumitomo Chemical Co., Ltd. Report No. QT-91-0011 Not GLP, Unpublished	N	SUM
IIA, 5.3.2/05	Cox, R.H.	1987	Amendment I to final report - Subacute dietary administration in dogs - S-3349 Sumitomo Chemical Co., Ltd. Report No. QT-71-0109 Not GLP, Unpublished	N	SUM
IIA, 5.3.2/06	Cox, R.H.	1988	Chronic toxicity study in dogs with S-3349 Sumitomo Chemical Co., Ltd. Report No. QT-81-0115 GLP, Unpublished	N	SUM

Annex No., Reference No.	Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	EU Data Protection Claimed (Y/N)	Owner
IIA, 5.3.2/07	Cox, R.H.	1993	Supplement to the final report (Correction pages) Sumitomo Chemical Co., Ltd. Report No. QT-31-0147 Not GLP, Unpublished	N	SUM
IIA, 5.3.2/08	Moore, M.R.	1993	Comments on the toxicological significance of hepatocytic pigment and on the no-adverse-effect-level (NOAEL) in a chronic toxicity study in dogs treated with S-3349 Sumitomo Chemical Co., Ltd. Report No. QT-31-0146 Not GLP, Unpublished	N	SUM
IIA, 5.3.2/09	Suzuki, T., Okuno, Y., Hiromori, T., Ito, S., Murakami, M., Kadota, T.	1978	Nine-month feeding study of S-3349 in mice Sumitomo Chemical Co., Ltd. Report No. QT-80-0005 Not GLP, Unpublished	N	SUM
IIA, 5.3.3/01	Gargus, J.L.	1986	21-day dermal toxicity study in rabbits with Rizolex, technical 97.7% [redacted] Report No. Not allocated Sumitomo Chemical Co., Ltd. Report No. QT-61-0142 GLP, Unpublished	N	SUM
IIA, 5.4.1/01	Moriya, M., Ohta, T., Shirasu, Y.	1981	S-3349: Microbial mutagenicity study Sumitomo Chemical Co., Ltd. Report No. QT-11-0019 Not GLP, Unpublished	N	SUM
IIA, 5.4.1/02	Suzuki, H., Miyamoto, J.	1978	Studies on mutagenicity of S-3349 with bacterial systems Sumitomo Chemical Co., Ltd. Report No. QT-80-0010 Not GLP, Unpublished	N	SUM
IIA, 5.4.1/03	Kogiso, S.	1990	*In vitro* chromosomal aberration test of Rizolex in Chinese hamster ovary cells (CHO-K1) Sumitomo Chemical Co., Ltd. Report No. QT-00-0134 GLP, Unpublished	N	SUM
IIA, 5.4.1/04	Monaco, M., Nunziata, A.	1981	Report of mutagenicity experiment performed on the test substance S-3349 of the Sumitomo Chemical Company, Limited of Osaka (Japan) Sumitomo Chemical Co., Ltd. Report No. QT-11-0044 Not GLP, Unpublished	N	SUM

Annex No., Reference No.	Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	EU Data Protection Claimed (Y/N)	Owner
IIA, 5.4.2/01	Suzuki, H.	1981	*In vivo* chromosomal aberration test of S-3349 on bone marrow cells of mice Sumitomo Chemical Co., Ltd. Report No. QT-10-0042 Not GLP, Unpublished	N	SUM
IIA, 5.4.2/02	Hara, M.	1990	*In vitro* unscheduled DNA synthesis (UDS) assay of Rizolex in rat hepatocytes Sumitomo Chemical Co., Ltd. Report No. QT-00-0135 GLP, Unpublished	N	SUM
IIA, 5.4.3/01	Brusick, D.J.	1981	Mutagenicity evaluation of S-3349 T.G. lot No. 4 in the rat dominant lethal assay Sumitomo Chemical Co., Ltd. Report No. QT-11-0018 Not GLP, Unpublished	N	SUM
IIA, 5.5/01	Pence, D.H., Serota, D.G., Alsaker, R.D., Koka, M., Banas, D.A., Dawkins, B.G., Kundzins, W.	1982	Chronic toxicity study in rats - S-3349 Sumitomo Chemical Co., Ltd. Report No. QT-21-0047 Not GLP, Unpublished	N	SUM
IIA, 5.5/02	Pence, D.H., Serota, D.G., Alsaker, R.D., Koka, M., Banas, D.A., Dawkins, B.G., Kundzins, W.	1983	Chronic toxicity study in rats - S-3349 - final report addendum Sumitomo Chemical Co., Ltd. Report No. QT-31-0053 Not GLP, Unpublished	N	SUM
IIA, 5.5/03	Seki, T., Hosokawa, S., Miyamoto, J.	1985	Comments on toxic effect and minimum effect level of S-3349 in chronic oral toxicity studies in rats Sumitomo Chemical Co., Ltd. Report No. QT-50-0090 Not GLP, Unpublished	N	SUM
IIA, 5.5/04	Pence, D.H, Phipps, N., Alsaker, R.D., Hepner, K.E., Spicer, K.M.	1985a	104-Week cholinesterase activity study in male and female rats - S-3349 Sumitomo Chemical Co., Ltd. Report No. QT-51-0077 Not GLP, Unpublished	N	SUM
IIA, 5.5/05	Satoh, R., Kashima, M., Satoh, H., Motoyama, M., Ishikawa, A.	1983	Twenty-four month chronic toxicity study of S-3349 in pulverized diet in mice Sumitomo Chemical Co., Ltd. Report No. QT-31-0061 Not GLP, Unpublished	N	SUM

Annex No., Reference No.	Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	EU Data Protection Claimed (Y/N)	Owner
IIA, 5.6.1/01	Pence, D.H., Wolfe, G.W., Hepner, K.E., Voelker, R.W., Ulland, B.M., Marshall, P.M., Cox, R.H.	1985b	Three-generation reproduction study in rats - S-3349 Sumitomo Chemical Co., Ltd. Report No. QT-51-0079 Not GLP, Unpublished	N	SUM
IIA, 5.6.1/02	Brusick, D.J.	1981	Mutagenicity evaluation of S-3349 T.G. lot No. 4 in the rat dominant lethal assay Sumitomo Chemical Co., Ltd. Report No. QT-11-0018 Not GLP, Unpublished ⇒ Annex IIA, 5.4.3/01	N	SUM
IIA, 5.6.2/01	Pence, D.H.	1979a	Teratology study in rats - S-3349 Sumitomo Chemical Co., Ltd. Report No. QT-01-0013 Not GLP, Unpublished	N	SUM
IIA, 5.6.2/02	Morseth, S.L.	1987	Teratology study of S-3349 T.G. in rats Sumitomo Chemical Co., Ltd. Report No. QT-71-0108 Not GLP, Unpublished	N	SUM
IIA, 5.6.2/03	Kashima, M.	1991	Teratology study of S-3349 in rabbits Sumitomo Chemical Co., Ltd. Report No. QT-11-0143 Not GLP, Unpublished	N	SUM
IIA, 5.7/01	Okuno, Y., Yamada, T., Hosokawa, S., Miyamoto, J.	1982	Acute delayed neurotoxicity study of S-3349 in hens Sumitomo Chemical Co., Ltd. Report No. QT-20-0060 Not GLP, Unpublished	N	SUM
IIA, 5.7/02	Takatsuka, M.	1985b	Validation - Acute delayed neurotoxicity study of S-3349 in hens Sumitomo Chemical Co., Ltd. Report No. QT-50-0089 Not GLP, Unpublished	N	SUM
IIA, 5.8.2/01	Segawa, T.	1978	Acute toxicity of S-3349 in rats and mice Sumitomo Chemical Co., Ltd. Report No. QT-71-0003 Not GLP, Unpublished ⇒ Annex IIA, 5.2.1/01	N	SUM
IIA, 5.9.1/01	Murayama, F.	1991	A review of medical examination of factory workers exposed to tolclofos-methyl Sumitomo Chemical Co., Ltd. Report No. QT-10-0144 Not GLP, Unpublished	N	SUM

Annex No., Reference No.	Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	EU Data Protection Claimed (Y/N)	Owner
IIA, 7.1.1/01	Segawa, T.	1981a	Acute oral toxicity study of S-3349 50% wettable powder in mice Sumitomo Chemical Co., Ltd. Report No. QT-11-0021 Not GLP, Unpublished	N	SUM
IIIA, 7.1.1/02	Segawa, T.	1981b	Acute oral toxicity study of S-3349 50% wettable powder in rats Sumitomo Chemical Co., Ltd. Report No. QT-11-0023 Not GLP, Unpublished	N	SUM
IIIA, 7.1.2/01	Segawa, T.	1981c	Acute dermal toxicity study of S-3349 50% wettable powder in mice Sumitomo Chemical Co., Ltd. Report No. QT-11-0020 Not GLP, Unpublished	N	SUM
IIIA, 7.1.2/02	Segawa, T.	1981d	Acute dermal toxicity study of S-3349 50% wettable powder in rats Sumitomo Chemical Co., Ltd. Report No. QT-11-0022 Not GLP, Unpublished	N	SUM
IIIA, 7.1.3/01	Eschbach J.C., Hogan, G.K.	1981	An acute inhalation toxicity study of S-3349 50WP in the rat Sumitomo Chemical Co., Ltd. Report No. QT-11-0016 Not GLP, Unpublished	N	SUM
IIIA, 7.1.4/01	Hara, S., Suzuki, T., Miyamoto, J.	1981a	Primary eye and skin irritation tests of S-3349 50% water-dispersible powder in rabbits Sumitomo Chemical Co., Ltd. Report No. QT-10-0030 Not GLP, Unpublished	N	SUM
IIIA, 7.1.5/01	Hara, S., Suzuki, T., Miyamoto, J.	1981a	Primary eye and skin irritation tests of S-3349 50% water-dispersible powder in rabbits Sumitomo Chemical Co., Ltd. Report No. QT-10-0030 Not GLP, Unpublished ⇒ Annex IIIA, 7.1.4/01	N	SUM
IIIA, 7.1.6/01	Hara, S., Suzuki, T., Miyamoto, J.	1981b	Skin sensitization test of S-3349 50% water-dispersible powder in guinea pigs Sumitomo Chemical Co., Ltd. Report No. QT-10-0031 Not GLP, Unpublished	N	SUM

Annex No., Reference No.	Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	EU Data Protection Claimed (Y/N)	Owner
IIIA, 7.2.1.1/01	Stevens, E.R., Davis, J.E.	1981	Potential exposure of workers during seed potato treatment with captan Bull, Environm, Contam. Toxicol. 26, 681-688 Not GLP Published	N	-
IIIA, 7.2.1.1/02	Lloyd, G.A., Bell, G.J., Richardson, P.	1980	Evaluation of operator hazards - ULV application of thiabendazole to potatoes on harvesting equipment Operator Protection Group Report No. SH/12 Not GLP Published	N	-
IIIA, 7.2.1.2/01	Jackson, C.M.	1995a	Tolclofos methyl dust 10% (Code: CR 17495) Rizolex: Potato treatment operator exposure study AgrEvo UK Limited Report No. TOX/94/192-61 Sumitomo Chemical Co., Ltd. Report No. QT-0151 GLP, Unpublished	N	AVS
IIIA, 7.2.1.2/02	Jackson, C.M.	1995b	1st amendment to report No TOX/94/192-61 Rizolex dust 10% Code: CR 17495 potato treatment operator exposure study AgrEvo UK Limited Report No. TOX/94/192-61 Sumitomo Chemical Co., Ltd. Report No. QT-0157 Not GLP, Unpublished	N	AVS
IIIA, 7.2.1.2/03	Burden, A.N.	1995	1st addendum to report S-3349/T77 tolclofos methyl dust 10% (Code: CR 17495) Rizolex: Potato treatment operator exposure study, analytical phase AgrEvo UK Limited Report No. 194/107-1012 Sumitomo Chemical Co., Ltd. Report No. QT-0158 Not GLP, Unpublished	N	AVS
IIIA, 7.2.1.2/04	Jackson, C.M.	1995c	1st amendment to addendum to report No TOX/94/192-61 (study No TOX93301) Rizolex dust 10% Code: CR 17495 operator exposure study, analytical phase AgrEvo UK Limited Report No. TOX/94/192-61 Sumitomo Chemical Co., Ltd. Report No. QT-0159 Not GLP, Unpublished	N	AVS
IIIA, 7.3/01	Savides, M.C.	2003	[^{14}C]Tolclofos-methyl 50% SC: *In vivo* dermal absorption in male Sprague-Dawley rats Sumitomo Chemical Co., Ltd. Report No. QM-0057 GLP, Unpublished	Y*	SUM

Annex No., Reference No.	**Author(s)**	**Year**	**Title Source Company Report No. GLP or GEP Status (where relevant) Published or not**	**EU Data Protection Claimed (Y/N)**	**Owner**
IIIA, 7.3/02	Ward, R.J.	2003	Tolclofos-methyl 500g/l SC formulation: *In vitro* absorption of tolclofos-methyl through human and rat epidermis Sumitomo Chemical Co., Ltd. Report No. QM-0056 GLP, Unpublished	Y*	SUM