PART 2

Section 3 Toxicological Studies and Exposure Data and Information

The example of a summary and assessment of data which follows is intended to illustrate the approach recommended for the preparation of *Tier II* summaries and assessments. The material included has not been critically assessed for its technical content. Although based on a real submission, the data included in the following summary and evaluation have been amended to protect the commercial interests of the owner of the data.

Applicants should be aware that these guidelines are intended to provide a degree of flexibility. Where in particular cases, it is more appropriate to present the data and information in another format, applicants may do so. In such cases it is recommended that the applicant discuss the format proposed with the Regulatory Authority of the Country to which application is to be made.

IIIA 7.1.1 Acute oral toxicity

Report: IIIA 7.1.1/01 Crown H 1996, Acute oral toxicity of OEC 2222 in rats, Report Number: CCC-14543

Guidelines

US EPA FIFRA Guideline § 81-1, which is equivalent to OECD 401 and EEC B1

GLP

Yes [22], but with the exception that the dosing solution was not analysed to verify concentration, homogeneity and stability of the vehicle. However, the dose was prepared freshly prior to dosing. This deviation did not compromise the acceptability of the study.

Executive Summary

In an acute oral toxicity study, groups of fasted, young adult Sprague-Dawley rats, 5/sex, were given a single oral dose of OEC 2222 (79.3 % chemx) suspended in corn oil at a dose level of x,xxx mg as/kg bw (xxx,xxx ppm) and were observed for 14 days.

Oral LD_{50}	males	=	> x,xxx mg as/kg bw (> xxx,xxx ppm)
	females	=	> x,xxx mg as/kg bw (> xxx,xxx ppm)
	combined	=	> x,xxx mg as/kg bw (> xxx,xxx ppm)

[22] In the US, laboratories are responsible for certifying that they have complied with FIFRA GLP requirements. The EPA (Environmental Protection Agency, Office of Compliance Monitoring) verifies compliance by means of periodic inspections.

OEC 2222 is of a low order of toxicity following exposure of rats by the oral route. Clinical signs consisting of salivation and moist rales were noted on the day of dosing in a few animals. Most animals were free of clinical signs throughout the study. There were no treatment related necropsy findings or changes in body weight). On the basis of this study, the test material does not warrant classification as being harmful or toxic.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** OEC 2222
   - **Description:** beige coloured water dispersible granule (80 % chemx)
   - **Lot/Batch #:** NPD-9501-6384-F
   - **Purity:** 79.3 % as [23]
   - **Stability of test compound:** shown to be stable in an accelerated storage stability test (14 days at 54 °C)

2. **Vehicle and/or positive control:** distilled water

3. **Test animals -**
   - **Species:** Rat
   - **Strain:** Sprague-Dawley (CD)
   - **Age:** Young adult
   - **Weight at dosing:** 227 - 276 g males; 215 - 265 females
   - **Source:** Charles River Laboratories, Portage, MI
   - **Acclimation period:** 7 days
   - **Diet:** Chow (#5001), *ad libitum*
   - **Water:** Tap water, *ad libitum*
   - **Housing:** Animals were individually housed in stainless steel suspended cages
   - **Environmental conditions -**
     - **Temperature:** Temperature was not specified
     - **Humidity:** Relative humidity ranged from 45 to 84 %
     - **Air changes:** Not recorded
     - **Photoperiod:** Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. **In life dates:** 5 to 29 October 1995

2. **Animal assignment and treatment**

   Animals were assigned to the test groups listed in Table IIIA 7.1.1-1. Following an overnight fast (17 - 22 hours), rats were given a single dose of test material, in distilled water by gavage at a limit dose of x,xxx mg as/kg bw (xxx,xxx ppm) to 5 male and 5 female rats using an application volume of xx mL/kg.
   Animals were observed for gross toxicity, behavioural changes and/or mortality at approximately 1, 2.5 and 4 hours after dosing and at least once daily for the remainder of the 14-day study. Body weights were recorded at day 0 (prior to dosing), 7 and 14. On day 14, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.

[23] Details with respect to the purity and content of impurities of the test material are provided in Document J

3. Statistics

The data were did not warrant statistical analysis.

II. RESULTS AND DISCUSSION

A. Mortality

Details are provided in Table IIIA 7.1.1-1. No mortalities occurred at xxxx mg/kg bw (xxx,xxx ppm), the only dose level tested.

Table IIIA 7.1.1-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Males	Females	Combined
0	0/5	0/5	0/10
x,xxx	0/5	0/5	0/10

The oral LD_{50} for males was > xxxx mg/kg bw (> xxx,xxx ppm)
for females was > xxxx mg/kg bw (> xxx,xxx ppm)
combined was > xxxx mg/kg bw (> xxx,xxx ppm)

B. CLINICAL OBSERVATIONS

Clinical signs consisting of salivation and moist rales were noted on the day of dosing in a few animals. Most animals were free of clinical signs throughout the study.

C. BODY WEIGHT

All animals had gained weight 7 and 14 days following dosing.

D. NECROPSY

No abnormalities were observed at gross necropsy.

E. DEFICIENCIES

None

III. CONCLUSIONS

The acute oral LD_{50} of OEC 2222 to rats was greater than xxxx mg/kg bw (xxx,xxx ppm). The preparation does not warrant classification as being toxic or harmful on the basis of its acute oral toxicity.

(Crown H 1996a)

IIIA 7.1.2 **Acute percutaneous (dermal) toxicity**

Report: IIIA 7.1.2/01 Crown H 1996, Acute dermal toxicity study in rats of OEC 2222, Report Number CCC-14544

Guidelines

US EPA FIFRA Guideline § 81-2, which is equivalent to OECD 402 and EEC B3

GLP: Fully GLP compliant [22]

Executive Summary

In an acute dermal toxicity study, groups of young adult Sprague-Dawley rats, 5/sex, were exposed by the dermal route to OEC 2222, a water dispersible granular preparation (79.3 % chemx) in distilled water for 24 hours to 10 % of body surface area at doses of 0 and x,xxx mg as/kg bw (xx,xxx ppm). Animals then were observed for 14 days.

Dermal LD_{50}	males	=	> x,xxx mg as /kg bw (> xx,xxx ppm)
	females	=	> x,xxx mg as/kg bw (> xx,xxx ppm)
	combined	=	> x,xxx mg as/kg bw (> xx,xxx ppm)

There were no treatment related clinical signs, necropsy findings or changes in body weight. On the basis of this study, the test material does not warrant classification as being harmful or toxic.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** OEC 2222
   - **Description:** beige coloured water dispersible granule (80 % chemx)
   - **Lot/Batch #:** NPD-9501-6384-F
   - **Purity:** 79.3 % as [23]
   - **Stability of test compound:** shown to be stable in an accelerated storage stability test (14 days at 54 °C)

2. **Vehicle and/or positive control:** test material dosed as received

3. **Test animals -**

Species:	Rat
Strain:	Sprague-Dawley (CD)
Age:	Young adult
Weight at dosing:	227 - 276 g males; 215 - 265 females
Source:	Charles River Laboratories, Portage, MI
Acclimation period:	7 days
Diet:	Chow (#5001), *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Animals were individually housed in stainless steel suspended cages
Environmental conditions -	
Temperature:	Temperature was not specified
Humidity:	Relative humidity ranged from 45 to 84 %
Air changes:	Not recorded
Photoperiod:	Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. **In life dates:** 5 to 29 October 1995

2. **Animal assignment and treatment**

Animals were assigned to the test groups listed in Table IIIA 7.1.2-1. On the day prior to dosing, the fur was clipped from the dorsal area of the trunk of each animal. The clipped area accounted for more than 10 % of each animal's body surface. The test substance was administered as a single occluded dermal application and was applied moistened with distilled water. After an exposure period of 24 hours, the occlusion was removed and residual test material was removed with distilled water. Animals were observed for gross toxicity and behavioural changes on three occasions on the day of dosing and once daily thereafter for the duration of the study. Mortality checks were conducted twice daily. Individual body weights were measured and recorded on days 1, 7 and 14. On day 14, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.

Table IIIA 7.1.2-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Males	Females	Combined
0	0/5	0/5	0/10
x,xxx	0/5	0/5	0/10

3. **Statistics**

The data were did not warrant statistical analysis.

II. RESULTS AND DISCUSSION

A. Mortality

Details are provided in Table IIIA 7.1.2-1. No mortalities occurred at xxxx mg/kg bw (xx,xxx ppm), the only dose level tested.

The dermal LD_{50}	for males was	> xxxx mg/kg bw (> xx,xxx ppm)
	for females was	> xxxx mg/kg bw (> xx,xxx ppm)
	combined was	> xxxx mg/kg bw (> xx,xxx ppm)

B. CLINICAL OBSERVATIONS

There were no clinical signs observed.

C. BODY WEIGHT

Weight gain was normal in all animals at the 7 and 14-day measurement intervals.

D. NECROPSY

No treatment related gross necropsy observations were noted.

E. DEFICIENCIES

None.

III. CONCLUSIONS

The acute percutaneous LD_{50} of OEC 2222 to rats was greater than xxxx mg/kg bw. The preparation does not classify as being toxic or harmful on the basis of its acute percutaneous toxicity.

(Crown H 1996b)

IIIA 7.1.3 Acute inhalation toxicity to rats

Report: IIIA 7.1.3/01 Crown H 1996, Acute inhalation study of OEC 2222, Report Number CCC-14545

Guidelines

US EPA FIFRA Guideline § 81-3, which is equivalent to OECD 403 and EEC B2

GLP

Yes [22] but with the exception that the stability of the test material was not determined. However, the dose was prepared freshly prior to dosing. This deviation did not compromise the acceptability of the study.

Executive Summary

In an acute inhalation toxicity study, groups of young adult Sprague-Dawley rats (5/sex) were exposed by the inhalation route to an aerosol of OEC 2222 (79.6 % chemx) for 4 hours to (nose only) at concentrations of 0 and x.x mg/L (x.x ppm), the maximum achievable concentration. Animals then were observed for 14 days.

LC_{50}	males	=	> x.x mg/L (> x.x ppm)
	females	=	> x.x mg/L (> x.x ppm)
	combined	=	> x.x mg/L (> x.x ppm)

During the first three days following exposure the following symptoms were observed: rapid respiration, rattling respiratory sounds, red/brown perinasal encrustation, periorbital encrustation and emaciation. All animals appeared normal on days 4 through 14. Weight gain was normal in all animals at the 2, 7 and 14-day measurement intervals. There were no exposure-related abnormalities observed during macroscopic examinations. On the basis of this study, the test material does not warrant classification as being harmful or toxic.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** OEC 2222
   - **Description:** beige coloured water dispersible granule (80 % chemx)
   - **Lot/Batch #:** NPD-9507-6721-F
   - **Purity:** 79.6 % as [23]
   - **Stability of test compound:** shown to be stable in an accelerated storage stability test (14 days at 54 °C)

2. **Vehicle and/or positive control:** OEC 2222 aerosol

3. **Test animals -**
   - **Species:** Rat
   - **Strain:** Sprague-Dawley (CD)
   - **Age:** Young adult
   - **Weight at dosing:** 269 - 295 g males; 236 - 261 females
   - **Source:** Charles River Laboratories, Portage, MI
   - **Acclimation period:** 8 days
   - **Diet:** Chow (#5002), *ad libitum*
   - **Water:** Tap water, *ad libitum*
   - **Housing:** Animals were individually housed in stainless steel suspended cages

Environmental conditions -

Temperature:	Temperature was not specified
Humidity:	Relative humidity ranged from 45 to 80 %
Air changes:	Not recorded
Photoperiod:	Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. In life dates: 5 February to 27 September 1995

2. Animal assignment and treatment

Animals were assigned to the test groups listed in Table IIIA 7.1.3-1. Animals were observed approximately hourly during the 4-hour exposure period. Thereafter mortality and moribundity checks were conducted twice daily. Observations for signs of toxicity were conducted immediately following exposure and daily thereafter. Individual body weights were measured and recorded on days 2, 7 and 14. On day 14, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.

Table IIIA 7.1.3-1 Doses, mortality / animals treated

Dose (mg/L) in xx L air / minute	Males	Females	Combined
0	0/5	0/5	0/10
x.x	0/5	0/5	0/10

3. Generation of the test atmosphere / chamber description

An 80-L nose only exposure chamber was used. During exposure (4 hours), individual plastic tubes were positioned in two tiers around the outside of the chamber such that only the nose of test animals was exposed to the interior of the chamber. A JET-O-MIZER® jet mill was used to mill the test material (OEC 2222) and generate the test aerosol. The test atmosphere was sampled at 20, 80, 140 and 223 minutes into the 240-minute exposure period. The samples were analysed by means of HPLC, using an xxxxxx column, 2 % acetonitrile mobile phase and UV (xx nm) detection. The limit of detection (LOD) for chemx was x µg as/L of air, while the limit of quantification (LOQ) was xx µg as/L of air. The test atmosphere concentration was x.x ± 0.16 mg as/L air (x.x ± 0.16 ppm).

Two samples were taken for particle size analysis using an Anderson cascade impactor. One of the samples was taken during the first part of the exposure period, the second during the second part of the exposure period:

mass median aerodynamic diameter: 3.6 microns
% particles < 10 microns: 92
% particles < 1 micron: 5

4. Statistics

The data were did not warrant statistical analysis.

II. RESULTS AND DISCUSSION

A. Mortality

Details are provided in Table IIIA 7.1.3-1. No mortalities occurred at x.x mg/L (x.x ppm), the only dose level tested.

The 4 hour inhalation LC_{50}	for males was	> x.x mg/L (> x.x ppm)
	for females was	> x.x mg/L (> x.x ppm)
	combined was	> x.x mg/L (> x.x ppm)

B. CLINICAL OBSERVATIONS

All animals appeared normal during the exposure period. Nasal and ocular discharges / encrustations were noted immediately following exposure. During the first three days following exposure the following symptoms were observed: rapid respiration, rattling respiratory sounds, red/brown perinasal encrustation, periorbital encrustation and emaciation. All animals appeared normal on day 4 through day 14.

C. BODY WEIGHT

Weight gain was normal in all animals at the 2, 7 and 14-day measurement intervals.

D. NECROPSY

There were no exposure-related abnormalities observed during macroscopic examinations.

E. DEFICIENCIES

None.

III. CONCLUSIONS

The four-hour Inhalation LC_{50} of OEC 2222 in rats was greater than x.x mg/L (x.x ppm) (the maximum achievable concentration). The preparation does not warrant classification as being toxic or harmful on the basis of its acute inhalation toxicity.

(Crown H 1996c)

IIIA 7.1.4 **Skin irritation**

Report: IIIA 7.1.4/01 Crown H 1996, 1996 Primary dermal irritation study in rabbits with OEC 2222, Report Number CCC-95-193

Guidelines

US EPA FIFRA § Guideline 81-5, which is equivalent to OECD 404, and EEC B4

GLP: Fully GLP compliant [22]

Executive Summary

In a primary dermal irritation study, groups of young adult New Zealand white rabbits (3/sex) were dermally exposed to 0.5 g of OEC 2222 (79.3% chemx) applied to 10 % of body surface area, for 4 hours. Animals then were observed for 72 hours. Irritation was scored using the Draize scheme.

Topical application of OEC 2222 to two sites in the dorsal region, maintained in contact with the skin for four hours with an occlusive dressing, provoked only slight erythema, with no oedema after one hour. Complete regression was observed within 48 hours following treatment. On the basis of this study, the test material does not warrant classification as being a skin irritant.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** OEC 2222
   - **Description:** beige coloured water dispersible granule (80 % chemx)
   - **Lot/Batch #:** NPD-9501-6384-F
   - **Purity:** 79.3 % as [23]
   - **Stability of test compound:** shown to be stable in an accelerated storage stability test (14 days at 54 °C)

2. **Vehicle and/or positive control:** test material dosed as received

3. **Test animals -**
   - **Species:** Rabbit
   - **Strain:** New Zealand
   - **Age:** Young adult
   - **Weight at dosing:** 2.1 to 2.s kg males; 2.1 to 2.5 kg females
   - **Source:** Chalk Cliff Rabbitry, Whitesville, MI
   - **Acclimation period:** 5 days
   - **Diet:** Chow (#5322), *ad libitum*
   - **Water:** Tap water, *ad libitum*
   - **Housing:** Animals were individually housed in stainless steel suspended cages

Environmental conditions -

Temperature:	Temperature was not specified
Humidity:	Relative humidity ranged from 40 to 84 %
Air changes:	Not recorded
Photoperiod:	Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. In life dates: 12 to 22 September 1995

2. Animal assignment and treatment

On the day prior to dosing, the fur was clipped from the dorsal area of the trunk of each animal using a small animal clipper. The test material was applied, semi-occluded, as a single dermal administration to three male and three female New Zealand White rabbits. The application rate was 0.5 g per animal. The substance was applied as a powder using moistened gauze. Two application sites per animal were used. After an exposure period of 4 hours, the occlusion was removed and residual test material was removed with distilled water. The test sites were examined for signs of erythema and oedema at 1, 24, 48 and 72 hours following patch removal.

II. RESULTS AND DISCUSSION

A. FINDINGS

Topical application of OEC 2222 to two sites in the dorsal region, maintained in contact with the skin for four hours with an occlusive dressing, provoked only slight erythema, with no oedema after one hour. Complete regression was observed within 48 hours following treatment. The average of the irritation indices at 24, 48 and 72 hours was xx and xx for erythema and oedema, respectively (Table IIIA 7.1.4-1).

Table IIIA 7.1.4-1 Irritation indices following topical application of OEC 2222 to the skin of New Zealand rabbits

		Time after administration (hours)			
Animal		0.5	24	48	72
♂ 1	oedema	0	0	0	0
	erythema	x	x	0	0
♂ 2	oedema	0	0	0	0
	erythema	x	x	0	0
♂ 3	oedema	0	0	0	0
	erythema	x	0	0	0
♀ 1	oedema	0	0	0	0
	erythema	x	0	0	0
♀ 2	oedema	0	0	0	0
	erythema	x	0	0	0
♀ 3	oedema	0	0	0	0
	erythema	x	0	0	0

III. CONCLUSIONS

The preparation caused slight reversible erythema, but does not warrant classification as a being a skin irritant on the basis of the skin irritation test results obtained.

(Crown H 1996d)

IIIA 7.1.5 **Eye irritation**

Report: IIIA 7.1.5/01 Crown H 1996, Primary eye irritation study in rats with OEC 2222, Report Number CCC-95-192

Guidelines

US EPA FIFRA Guideline § 81-4, which is equivalent to OECD 405 and EEC B5

GLP: Fully GLP compliant[22]

Executive Summary

In a primary eye irritation study, xx mg of OEC 2222 (79.3 % chemx) in distilled water was instilled into the conjunctival sac of the right eye of 6 young adult New Zealand white rabbits (2 females and 4 males). Animals then were observed for 7 days. Eye irritation was scored using the Draize scheme for unwashed eyes.

There were no observed effects on the iris or the cornea in any animals at any time after instillation of the test material. Slight reddening of the conjunctiva was observed in 6/6 animals one hour after instillation with progressive and complete regression in five animals by 48 hours and in the sixth rabbit by 72 hours post exposure. Slight-to-moderate conjunctival chemosis and / or discharge occurred in most animals, but were completely resolved 24 hours after exposure. The mean irritation indices at 24, 48 and 72 hours for the six animals were xx for reddening of the conjunctiva and xx for chemosis and lesions of the iris and cornea. On the basis of this study, the test material does not warrant classification as being an eye irritant.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** OEC 2222
   - **Description:** beige coloured water dispersible granule (80 % chemx)
   - **Lot/Batch #:** NPD-9501-6384-F
   - **Purity:** 79.3 % as [23]
   - **Stability of test compound:** shown to be stable in an accelerated storage stability test (14 days at 54 °C)

2. **Vehicle and/or positive control:** test material dosed in distilled water

3. Test animals -

Species:	Rabbit
Strain:	New Zealand
Age:	Young adult
Weight at dosing:	2.4 to 2.8 kg
Source:	Chalk Cliff Rabbitry, Whitesville, MI
Acclimation period:	5 days
Diet:	Chow (#5322), *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Animals were individually housed in stainless steel suspended cages
Environmental conditions -	
Temperature:	Temperature was not specified
Humidity:	Relative humidity ranged from 35 to 84 %
Air changes:	Not recorded
Photoperiod:	Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. In life dates: 11 October to 24 October 1995

2. Animal assignment and treatment

Test material, mixed with distilled water, was instilled into the conjunctival sac of the right eye of each of six (two females and four males) NZW rabbits (xx mg test material per animal). The contralateral eyes served as controls for the animals used. This was followed by a 7-day observation period. Both eyes of each animal were examined for signs of irritation at 1, 24, 48 and 72 hours and 7 days after dosing. Scoring was carried out in accordance with the Draize method. Flourescein dye retention was assessed at 24 hours and at each subsequent interval until a negative response was obtained.

II. RESULTS AND DISCUSSION

A. FINDINGS

The formulation (OEC 2222) was found to be slightly irritating to the rabbit eye after instillation of xx mg (the volume equivalent of x.x ml of the undiluted product) into the conjunctival sac (Table IIIA 7.1.5-1). There were no observed effects on the iris or the cornea in any animals at any time after instillation of the test material. Slight reddening of the conjunctiva was observed in 6/6 animals one hour after instillation with progressive and complete regression in five animals by 48 hours and in the sixth rabbit by 72 hours post exposure. Slight-to-moderate conjunctival chemosis and/or discharge occurred in most animals, but were completely resolved by 24 hours after exposure. The mean irritation indices at 24, 48 and 72 hours for the six animals were xx for reddening of the conjunctiva and xx for chemosis and lesions of the iris and cornea.

Table IIIA 7.1.5-1 Irritation indices following installation of OEC 2222 into the conjunctival sac of New Zealand rabbits

			Time after administration. (hours)			
Animal			1	24	48	72
♂ 1	conjunctiva	oedema	x	0	0	0
		erythema	x	x	0	0
	iris		0	0	0	0
	cornea		0	0	0	0
♂ 2	conjunctiva	oedema	x	0	0	0
		erythema	x	x	0	0
	iris		0	0	0	0
	cornea		0	0	0	0
♂ 3	conjunctiva	oedema	x	0	0	0
		erythema	x	x	1	0
	iris		0	0	0	0
	cornea		0	0	0	0
♂ 4	conjunctiva	oedema	x	0	0	0
		erythema	x	x	0	0
	iris		0	0	0	0
	cornea		0	0	0	0
♀ 1	conjunctiva	oedema	x	0	0	0
		erythema	x	x	0	0
	iris		0	0	0	0
	cornea		0	0	0	0
♀ 2	conjunctiva	oedema	x	0	0	0
		erythema	x	x	0	0
	iris		0	0	0	0
	cornea		0	0	0	0

III. CONCLUSIONS

On the basis if the test results obtained, the preparation OEC 2222 does not warrant classification as being an eye irritant.

(Crown H 1996e)

IIIA 7.1.6 **Skin sensitization**

Report: IIIA 7.1.6/01 Crown H 1996, Guinea pig maximization test with OEC 2222 (Method of Magnusson and Kligman), Report Number CCC-95-194

Guidelines

US EPA FIFRA Guideline § 81-6, which is equivalent to OECD 406 and EEC B6

GLP: Fully GLP compliant [22]

Executive Summary

In a dermal sensitization study with OEC 2222 (79.3 % chemx) in polypropylene glycol and in Freund's Complete Adjuvant (FCA) emulsion, 20 young adult Dunkin Hartley albino guinea pigs (10/sex) were subjected to testing. The treatment regime involved induction of sensitization by intradermal injection on day 1, induction of sensitization by topical administration on day 8 and challenge by topical administration on day 22

No clinical abnormalities were observed during the study and except for one female which was found dead on day 10, all animals survived and gained weight throughout the study. No abnormalities were observed upon macroscopic post-mortem examination of the dead animal (normal lesions from dosing were seen on the animal's back). The death of this animal does not appear to have been due to administration of the test material. On the basis of this study, the test material does not warrant classification as being a skin sensitizer.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** OEC 2222
   - **Description:** beige coloured water dispersible granule (80 % chemx)
   - **Lot/Batch #:** NPD-9501-6384-F
   - **Purity:** 79.3 % as [23]
   - **Stability of test compound:** shown to be stable in an accelerated storage stability test (14 days at 54 °C)

2. **Vehicle and/or positive control:** polypropylene glycol, Freund's Complete Adjuvant (FCA) emulsion and saline 9 %

3. **Test animals -**
   - **Species:** Albino Guinea Pigs
   - **Strain:** Dunkin Hartley Haz:(DH)FBR
   - **Age:** 5 to 7 weeks at dosing
   - **Weight at dosing:** 345 to 420 g males; 270 to 435 g females
   - **Source:** GTP, Gainsville, Pa
   - **Acclimation period:** 14 days
   - **Diet:** Agway Prolab Purina Guinea Pig Diet, *ad libitum*
   - **Water:** Tap water, *ad libitum*
   - **Housing:** Animals were individually housed in stainless steel suspended cages with wire mesh bottoms
   - **Environmental conditions -**
     - **Temperature:** 18 to 24 °C
     - **Humidity:** Relative humidity ranged from 30 to 60 %
     - **Air changes:** Not recorded
     - **Photoperiod:** Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS:

1. **In life dates:** 11 January to 15 February 1996

2. Animal assignment and treatment

The treatment regime involved induction of sensitization by intradermal injection on day 1, induction of sensitization by topical administration on day 8 and challenge by topical administration on day 22. The test levels for dermal and intradermal inductions and challenge were selected following preliminary irritancy testing. The sites were pre-treated with 10 % sodium lauryl sulphate to elicit some dermal response, because of the known non-irritancy of the test substance. Propylene glycol was used alone for intradermal induction and mixed with chemx to produce a 5 % w/v mixture for intradermal induction. Freund's Complete Adjuvant (FCA) Emulsion was mixed 50 % v/v in distilled water for intradermal induction and mixed with chemx to produce a 5 % w/v mixture for intradermal induction. 0.9 % saline was used alone for topical induction and challenge and also used to moisten OEC 2222 for topical induction and challenge. The test material was administered at a concentration of 5 % for the intradermal induction and at 100 % for the topical induction to 20 Dunkin Hartley guinea pigs (10 male and 10 female).

II. RESULTS AND DISCUSSION

A. FINDINGS

No clinical abnormalities were observed during the study and except for one female which was found dead on day 10, all animals survived and gained weight throughout the study. No abnormalities were observed upon macroscopic post-mortem examination of the dead animal (normal lesions from dosing were seen on the animal's back). The death of this animal does not appear to have been due to administration of the test material.

Following administration of the topical challenge dose, all 19 test animals and 10 irritation control animals were free of irritation responses at challenge (two animals had scores of 0.5). The severity indices for test animals at 24 and 48 hours were 0.1 and 0.0, respectively, compared with 0.0 at 24 and 48 hours for the irritation control animals. The incidence index of sensitisation to the test material at challenge was 0 %.

III. CONCLUSIONS

On the basis of the test results obtained, the preparation (OEC 2222) does not warrant classification as being a dermal sensitizer.

(Crown H 1996f)

IIIA 7.1.7 Supplementary studies for combinations of plant protection products

No studies in combination with other plant protection products are necessary as its use in combination with other plant protection products, as a tank mix is not proposed.

IIIA 7.1.8 Summary of acute toxicity of OEC 2222

Type of study	**Vehicle**	**Results)**	**Reference**
Oral route – rat	distilled water	LD_{50} > xxxx mg /kg bw	IIIA 7.1.1/01 Crown H 1996a
Percutaneous route – rat	none	LD_{50} > xxxx mg /kg bw	IIIA 7.1.2/01 Crown H 1996b
Inhalation route – Rat	none	LC_{50} > x.x mg / L air *	IIIA 7.1.3/01 Crown H 1996c
Skin irritation – rabbits	none	non-irritating	IIIA 7.1.4/01 Crown H 1996d
Eye irritation – rabbits	none	non irritating	IIIA 7.1.5/01 Crown H 1996e
Skin sensitization - guinea pig	Propylene glycol, Freund's Complete Adjuvant (FCA) emulsion and saline	non-sensitizing	IIIA 7.1.6/01 Crown H 1996f

* maximum achievable concentration

OEC 2222 has a low acute toxicity by the oral, percutaneous and inhalation routes of administration. OEC 2222 is not an eye or a skin irritant and is not a skin sensitizer.

IIIA 7.2 Short-term toxicity studies

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IIIA 7.3.1 Estimation of operator exposure, assuming personal protective equipment is not used

IIIA 7.3.1.1 Estimation using European exposure models

Report: IIIA 7.3.1/01 Seacombe H 1996, Estimation using European models of operator exposure (mixer / loader / applicator), for OEC 2222 without use of protective clothing and equipment, Report Number CCC-96-4623

Exposure Models

Exposure to the product was estimated using both the German model [24] and the UK model [25].

Estimations (protective clothing not worn)

The estimated operator exposure values determined using a worst case scenario, assuming protective clothing was not worn are provided in Table IIIA 7.3.1-1. Operator exposure is related to the AOEL, to provide an estimate of the extent to which the AOEL is accounted for. The proposed AOEL for chemx is xxx mg as/kg body weight/day, based on a sub-chronic NOEL of xxx mg/kg/day (90-day oral dog study) and a 100-fold safety factor.

Table IIIA 7.3.1.1-1 Estimations of operator exposure in relation to the AOEL - no protective clothing and equipment used

Model	70 kg Operator Exposure mg/kg bw per day	% of AOEL used
German Model	0.0064	x.xx %
UK Model	0.577	xx.x %

The calculations show that in the worst case approximately xx % of the AOEL is used (UK model smallest pack size, 200 L/ha, 50 ha / day, and no protective clothing).

Scenario used

The following points, which are specific to OEC 2222, have been taken into account for the purposes of calculation. For each model only the worst case scenario as described below, has been addressed -

i the product will be packed in dose sachets in sizes from 25 g to 125 g (1 to 5 hectare packs). The sachets are not water-soluble. The 1 ha pack (25 g) is the worst case with respect to operator exposure in the UK model as this maximises the number of opening operations,

ii the maximum application rate used will be 25g product per hectare (20g as / ha),

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

[25] 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) 1992

iii the application spray volume will be 200 to 250 litres per hectare, 200 litres being the worst case for operator exposure as this is the most concentrated spray solution,

iv a work rate of 50 hectares per day has been used - this is higher than usual for the German model but makes the model inputs closer to being equivalent, and

v in the absence of specific data on chemx, the UK model requires use of a 10 % percutaneous absorption default value and 1 % default value for penetration through gloves (based on OEC 2222 being a solid formulation).

Calculations

The actual calculations are presented in Tables IIIA 7.3.1.1-2 and IIIA 7.3.1.1-3. The calculations were made assuming operators weighed 70 kg, 10 kg higher than is normally used for the UK model. It is believed that the higher figure represents a more realistic weight for operators. Use of that figure serves to make the model inputs closer to being equivalent.

Table IIIA 7.3.1.1-2 Estimation of operator exposure in relation to the AOEL - German model

Product :		OEC 2222			**Formulation Type :**		WDG			
Active substance :		Chemx			**Concentration :**		800	g/litre or kg		
NOEL :		Xxx	mg/kg/day							
Maximum Rate :			0.025	kg/ha	**Area treated per day:**			50	ha	
Amount of as handled /day =			50	ha	x	0.02	kg as/ha	=	1	kg as /day
Exposure for :				**tractor sprayer with cab, low growing crop**						
Im	=	0.0006	mg/kg as	x	1	=	0.0006	mg / person /day		
Ia	=	0.001	mg/kg as	x	1	=	0.001	mg / person /day		
Da(c)	=	0.06	mg/kg as	x	1	=	0.06	mg / person /day		
Da(h)	=	0.38	mg/kg as	x	1	=	0.38	mg / person /day		
Da(b)	=	1.6	mg/kg as	x	1	=	1.6	mg / person /day		

Exposure without protective clothing and equipment

Dm	=	2.4	mg/kg as	x	1	=	2.4	mg / person /day

Estimated Exposure mg / person /day

Inhalation	mix/load	0.0006		
	spray	0.001		
Dermal	mix /load	2.4		
	spray	2.04		
Systemic	mix / load	0.24	assuming 10.0%	absorption (10% unless data to suggest otherwise)
	spray	0.204		
	TOTAL	**0.4456**	**mg / person / day**	

for 70 kg man = **0.0064** mg /kg body weight/day

Xxxxx fold safety factor

Table IIIA 7.3.1.1-3 Estimation of operator exposure in relation to the AOEL, where protective clothing and equipment are not used - UK model (percent absorption method)

A PRODUCT DATA

1	Name :	OEC 2222	
2a	Active substance :	Chemx	
2b	Concentration :	800	mg/g
3	Formulation type :	WG	
4a	Main solvent :		
4b	Concentration of solvent :		% w/w
5	Maximum in-use as concentration :	0.1	mg/ml

B EXPOSURE DURING MIXING AND LOADING

1a	Container Size :	0.025	kg
1b	Hand	0.01	g / operation
2	Application rate :	0.025	kg product / ha
3	Work rate :	50	ha / day
4	No of operations per day :	50	/ day
5	Contamination / day :	0.5	g / day
6	Protective clothing :	None	
7	Penetration of gloves :	100	%
8	Dermal exposure to	0.5	g / day

C EXPOSURE DURING SPRAY APPLICATION

1	Application technique :	Vehicle mounted (with cab) hydraulic nozzles.		
2	Application volume :	200		litres spray / ha
3	Volume of surface	10		ml/h
		HANDS	TRUNK	LEGS
4	Distribution :	65 %	10 %	25 %
5	Clothing :	None	permeable	permeable
6	Penetration :	10 %	5 %	15 %
7	Dermal exposure :	6.5 ml/h	0.05 ml/h	0.375 ml/h
8	Duration of exposure :	6		hours
9	Total dermal exposure to spray :	41.55		ml / day

D SYSTEMIC EXPOSURE

		mixing and loading		spray application	
1	Dermal exposure	0.5	g / day	41.55	ml/day
2	Concentration of as	800	mg/g	0.1	mg/ml
3	Dermal Exposure to as	400	mg/day	4.155	mg/day
4	Percent Absorption	10	%	10	%
5	Absorbed Dose	40	mg/day	0.4155	mg/day

Table IIIA 7.3.1.1-3 Continued)

E	**INHALATION EXPOSURE DURING SPRAY APPLICATION**			
	1	Inhalation exposure :	0.01	ml/h
	2	Duration of exposure :	6	hours
	3	Concentration of as :	0.1	mg/ml
	4	Inhalation exposure to as :	0.006	mg/day
	5	Percent absorbed :	100	%
	6	Absorbed Dose	0.006	mg/day
F	**PREDICTED EXPOSURE**			
	1	Total dose absorbed	40.42	mg / day
	2	Operator body weight	70	kg
	3	Operator Exposure	0.577	mg / kg body weight
G	**TOXICITY EXPOSURE RATIO**			
	1	Toxicological NOEL	Xxx	mg/kg body weight
	2	Toxicity : exposure ratio	Xxx.xxx	

CONCLUSIONS

Operator exposure to OEC 2222, during mixing, loading and spraying does not involve a significant risk to the health of the operators concerned, even where protective clothing and equipment used in normal agricultural practice, are not used.

(Seacombe H 1996a)

IIIA 7.3.1.2 **Estimation using the North American exposure model**

Exposure of persons handling products is generally estimated using the North American model [26]. To estimate total dermal and inhalation exposure for ground boom application, appropriate subsets of A and B grade data are created from the mixer / loader and from the applicator PHED database files.

PHED does not contain sufficient data to estimate mixer / loader exposure without gloves. Accordingly, estimates of exposure, assuming personal protective equipment were not used, were not prepared. The protective clothing specified on the proposed label for applicators and other handlers are long sleeved shirts, long pants, shoes and socks. Exposure estimates for mixer / loaders wearing long pants, long sleeved shirts and gloves, and for applicators wearing long pants, long sleeved shirts and no gloves are provided at point IIIA 7.3.2.2.

[26] Pesticide Handlers Exposure Database, Version 1.1, Versar Incorporated, prepared for the PHED Task Force, representing Health Canada, and the U.S. Environmental Protection Agency, February 1995

IIIA 7.3.2 Estimation of operator exposure, assuming personal protective equipment is used

IIIA 7.3.2.1 Estimation using European exposure models

Report: IIIA 7.3.2/01 Seacombe H 1996, Estimation using European models of operator exposure (mixer / loader / applicator), for OEC 2222, with use of protective clothing and equipment, Report Number CCC-96-4624

Exposure Models

Exposure to the product was estimated using the German model [24] and the UK model [25].

Estimations (protective clothing worn)

The estimated operator exposure values determined using the model scenarios, assuming protective clothing was worn during mixing and loading but not during spray application, is provided in Table IIIA 7.3.2.1-1. Operator exposure is related to the AOEL, to provide an estimate of the extent to which the AOEL is accounted for. The proposed AOEL for chemx is xxx mg as /kg body weight/day, based on a sub-chronic NOEL of xxx mg/kg/day (90-day oral dog study) and a 100 fold safety factor.

Table IIIA 7.3.2.1-1 Estimations of operator exposure in relation to the AOEL - protective clothing and equipment used

Model	70 kg Operator Exposure mg/kg bw per day	% of AOEL used
German Model	0.0033	x.x %
UK Model	0.012	x.x %

The calculations show that in the worst case, where protective clothing and equipment is used during loading and mixing, only some x % of the AOEL is used (UK model smallest pack size, 200L/ha, 50 ha / day).

Scenario used

The following points, which are specific to OEC 2222, have been taken into account for the purposes of calculation. For each model only the worst case scenario as described below, has been addressed -

i the product will be packed in dose sachets in sizes from 25 g to 125 g (1 to 5 hectare packs). The sachets are not water-soluble. The 1 ha pack (25 g) is the worst case with respect to operator exposure in the UK model as this maximises the number of opening operations,

ii the maximum application rate used will be 25 g product per hectare (20g as / ha),

iii the application spray volume will be 200 to 250 litres per hectare, 200 litres being the worst case for operator exposure as this is the most concentrated spray solution,

iv a work rate of 50 hectares per day has been used - this is higher than usual for the German model but makes the model inputs closer to being equivalent, and

v in the absence of specific data on chemx, the UK model requires use of a 10 % percutaneous absorption default value and 1 % default value for penetration through gloves (based on OEC 2222 being a solid formulation).

Calculations

The actual calculations are presented in Tables IIIA 7.3.2.1-2 and IIIA 7.3.2.1-3. The calculations are made assuming operators weighed 70 kg, 10 kg higher than is normally used for the UK model. It is believed that the higher figure represents a more realistic weight for operators. Use of that figure serves to make the model inputs closer to being equivalent.

Table IIIA 7.3.2.1-2 Estimation of operator exposure in relation to the AOEL - German model

Product :		OEC 2222			**Formulation Type :**		WDG			
Active substance :		Chemx			**Concentration** :		800	g/litre or kg		
NOEL :		Xxx	mg/kg/day							
Maximum Rate :		0.025	kg/ha		**Area treated per day:**		50	ha		
Amount of as handled /day =		50	ha	x	0.02	kg as/ha	=	1	kg as /day	
Exposure for :				**Tractor sprayer with cab, low growing crop**						
Im	=	0.0006	mg/kg as	x	1	=	0.0006	mg / person /day		
Ia	=	0.001	mg/kg as	x	1	=	0.001	mg / person /day		
Da(c)	=	0.06	mg/kg as	x	1	=	0.06	mg / person /day		
Da(h)	=	0.38	mg/kg as	x	1	=	0.38	mg / person /day		
Da(b)	=	1.6	mg/kg as	x	1	=	1.6	mg / person /day		

Exposure with protective clothing and equipment during mixing and loading

Dm	=	0.1 x 2.4	mg/kg as	x	1	=	0.24	mg / person /day

Estimated Exposure mg / person /day

Inhalation	mix/load	0.0006			
	Spray	0.001			
Dermal	mix /load	0.24			
	Spray	2.04			
Systemic	mix / load	0.024	assuming	10.0%	absorption (10% unless data to suggest otherwise)
	Spray	0.204			
	TOTAL	**0.2296**	**mg / person / day**		

For 70 kg man = **0.0033** mg /kg body weight/day

xxxxx fold safety factor

Table IIIA 7.3.2.1-3 Estimations of operator exposure in relation to the AOEL, where protective clothing and equipment are used during mixing and loading - UK model (percent absorption method)

A	**PRODUCT DATA**		
1	Name :	OEC 2222	
2a	Active substance :	chemx	
2b	Concentration :	800	mg/g
3	Formulation type :	WG	
4a	Main solvent :		
4b	Concentration of solvent :		% w/w
5	Maximum in-use as concentration :	0.1	mg/ml
B	**EXPOSURE DURING MIXING AND LOADING**		
1a	Container Size :	0.025	kg
1b	Hand	0.01	g / operation
2	Application rate :	0.025	kg product / ha
3	Work rate :	50	ha / day
4	No of operations per day :	50	/ day
5	Contamination / day :	0.5	g / day
6	Protective clothing :	gloves	
7	Penetration of gloves :	1	%
8	Dermal exposure to	0.005	g / day
C	**EXPOSURE DURING SPRAY APPLICATION**		
1	Application technique :	Vehicle mounted (with cab) hydraulic nozzles.	
2	Application volume :	200	litres spray / ha
3	Volume of surface	10	mL/h

	HANDS	TRUNK	LEGS
4 Distribution :	65 %	10 %	25 %
5 Clothing :	None	permeable	Permeable
6 Penetration :	10 %	5 %	15 %
7 Dermal exposure :	6.5 ml/h	0.05 ml/h	0.375 ml/h

8	Duration of exposure :	6	hours
9	Total dermal exposure to spray :	41.55	ml / day

D	**SYSTEMIC EXPOSURE**				
		mixing and loading		spray application	
1	Dermal exposure	0.005	g / day	41.55	ml/day
2	Concentration of as	800	mg/g	0.1	mg/ml
3	Dermal Exposure to as	4	mg/day	4.155	mg/day
4	Percent Absorption	10	%	10	%
5	Absorbed Dose	0.4	mg/day	0.4155	mg/day

Table IIIA 7.3.2.1-3 (Continued)

E	**INHALATION EXPOSURE DURING SPRAY APPLICATION**			
	1	Inhalation exposure :	0.01	ml/h
	2	Duration of exposure :	6	hours
	3	Concentration of as :	0.1	mg/ml
	4	Inhalation exposure to as :	0.006	mg/day
	5	Percent absorbed :	100	%
	6	Absorbed Dose	0.006	mg/day
F	**PREDICTED EXPOSURE**			
	1	Total dose absorbed	0.82	mg / day
	2	Operator body weight	70	kg
	3	Operator Exposure	0.012	mg / kg body weight
G	**TOXICITY EXPOSURE RATIO**			
	1	Toxicological NOEL	xxx	mg/kg body weight
	2	Toxicity : exposure ratio	xxx.xxx	

CONCLUSIONS

Operator exposure to OEC 2222, during mixing, loading and spraying does not involve a significant risk to the health of the operators concerned. Where protective clothing and equipment, as used in normal agricultural practice, are used, the risks arising are further minimised.

(Seacombe H 1996b)

IIIA 7.3.2.2 **Estimation using the North American model**

Report: IIIA 7.3.2/02 Seacombe H 1996, Estimation using the North American model (PHED) of operator exposure (mixer / loader / applicator), for OEC 2222, Report Number CCC-96-4625

Exposure model and scenarios

Exposure to OEC222, a dry flowable formulation of chemx, was estimated in relation to mixing, loading and application using a ground boom sprayer. Exposure was estimated using the Pesticide Handler Exposure Database (PHED) Version 1.1 [26]. PHED is a compilation of generic mixer / loader / applicator and flagger passive dosimetry data with associated software that facilitates the generation of scenario specific exposure estimates.

To estimate total dermal and inhalation exposure for ground boom application, appropriate subsets of A and B grade data were created from the mixer / loader and from the applicator PHED database files. There were no relevant data available in the mixer / loader / applicator database file. The mixer / loader file was subset for open mixing, dry flowable formulations and to exclude replicates for packaging in water soluble packets. The applicator file was subset for application by ground boom tractor or truck with open cabs. The number of replicates for inhalation and dermal data were acceptable. In the PHED subsets, the mean and range of the

pesticide mixed and applied and the sampling time were of the same order of magnitude as the estimated 8.8 kg as/d handled by a farmer treating 440 ha with 20 g as/ha in an 8-h work day.

Protective clothing and equipment specified on the proposed label for applicators and other handlers are long-sleeved shirts, long pants, shoes and socks. PHED does not contain sufficient data to estimate mixer / loader exposure without gloves, therefore exposure was estimated for mixer / loaders wearing long pants, long-sleeved shirts and gloves, and for applicators wearing long pants, long sleeved shirts and no gloves. PHED Version 1.1 uses actual data and does not assume clothing penetration factors.

All data were normalised for kg of as handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency, *i.e.* on summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part (arithmetic mean if normal distribution, geometric mean if lognormal distribution, median if any other distribution). Exposure estimates were based on farmers mixing / loading or applying OEC 2222 at 20 g as/ha to 440 ha/day, and custom (contract) applicators mixing / loading or applying OEC 2222 at 20 g as/ha to 2,700 ha/day.

Exposure was predominantly dermal. As no percutaneous absorption data were available, the default assumption was 100% absorption.

PHED Subsets

PHED subsets were created from the mixer / loader and from the applicator database files. The PHED subsets generated compare well with the proposed use scenario for OEC 2222 (Table IIIA 7.3.2.2-1)

Table IIIA 7.3.2.2-1 Comparison of PHED subsets with product use scenario

Parameter	Actual (specify source if not label)	PHED Subset		
		Mixer / loader	Applicator	Mixer / loader / applicator
Description of product:				
Formulation type	Dry flowable	Dry flowable	Not Relevant	Not applicable
Packaging type	Bags with measuring guide	Excludes water soluble bags	Not Relevant	Not applicable
Packet size	4 kg	Not Relevant	Not Relevant	Not applicable
Application volume	200 - 1000 L/ha	Not Relevant	Not Relevant	Not applicable
Use scenario:				
Crop types / Location	**Wheat**	Outdoor	Outdoor	Not applicable
Mixing procedure	Open mixing	Open mixing	Not Relevant	Not applicable
Application equipment	Ground boom	Not Relevant	Ground boom tractor or truck; open cab (or closed with window)	Not applicable

Table IIIA 7.3.2.2-1 (Continued)

Parameter	Actual (specify source if not label)	PHED Subset		
		Mixer / loader	Applicator	Mixer / loader / applicator
Clothing / personal protective equipment	Applicators: none Mixer / loaders: Overalls, goggles or face shield, chemical resistant gloves	Long pants, long sleeve shirts, gloves	Long pants, long sleeve shirts, no gloves	Not applicable
Application rate	20 g as/ha	Not Relevant	Not subset	Not applicable
active substance / applied	Farmers: 8.8 kg as/day (20 g as/ha x 440 ha) Custom applicators: 54 kg as/day (20 g as/ha x 2700 ha)	Arithmetic means: Dermal: 11.2 (2.2 - 46.8) Hands: 18.6 (2.2 – 59.4) Inhalation: 9.6 (2.2-29.4)	Arithmetic means: Dermal: 27.4 (1.6 - 111.6) Hands: 33.2 (1.6 - 112.8) Inhalation: 34.8 (5.4-111.6)	Not applicable
Sampling time (hours)	Typical work day is 8 hours 1 hour mixing & loading, 7 hours applying	Arithmetic means: Dermal: 7.4 (1.2 - 10.8) Hands: 8.8 (4.4 - 16.2) Inhalation: 7.8 (4.4 - 10.8)	Arithmetic means: Dermal: 4.6 (1.0 - 11.0) Hands: 7.0 (1.0 - 18.6) Inhalation: 5.8 (1.0 - 10.6)	Not applicable
Data quality	Not Relevant	Dermal: Not Relevant Hands: Not Relevant Inhalation: Not Relevant	Dermal: Not Relevant Hands: Not Relevant Inhalation: Not Relevant	Not applicable
Number of replicates	Not Relevant	Dermal: 16 – 24 (0 - feet) Hands: 21 Inhalation: 23	Dermal: 23 - 40 (0 - feet) Hands: 29 Inhalation: 22	Not applicable

Estimations

Estimates generated using PHED data, normalised to kg as handled, are presented in Tables IIIA 7.3.2.2-2 and IIIA 7.3.2.2-3. Scenario specific exposure estimates are presented in Tables IIIA 7.3.2.2-4 and IIIA 7.3.2.2-5. The estimations reported were prepared using two measures of central tendency - arithmetic means and the "best-fit". The "best fit" estimate is based on summing the measure of central tendency for each body part that is most appropriate to the distribution of the data for that body part (*i.e.* arithmetic mean if normal distribution, geometric mean if lognormal distribution, median if any other distribution). Both sets of estimates are presented to facilitate review sharing

It should be noted that estimates produced using the German model are geometric means while estimates generated using the UK model are 75th percentile values (see point IIIA 7.3.1.2). PHED arithmetic mean

values approximates the 70th percentile and can be considered the most suitable measure to compare with the UK model. In comparing estimates of exposure generated using the North American and European models, it is necessary that corrections be made to take account of the different scenarios applicable.

Table IIIA 7.3.2.2-2 Raw PHED exposure estimates based on arithmetic means

Ground boom application	mg as / kg as handled (arithmetic mean)						
	Dermal Body	Dermal Hands	Dermal Total	Dermal Absorbed[a]	Inhalation	Inhalation + Dermal Total [c]	Inhalation + Dermal Absorbed
PHED mixer / loader file	871	43	914	914	5	919	919
PHED applicator file	83.8	201.6	285.4	285.4	8.6	294	294
PHED mixer / loader / applicator file	954.8	244.6	1,199.4	1,199.4	13.6	1,213	1,213

[a] total dermal dose x percentage dermal absorption (default value of 100 % used)

[b] "best fit" estimate based on adding arithmetic means for normal distributions, geometric means for lognormal distributions and medians for other distributions.

[c] dermal absorption data should not be used if a dermal toxicity value is used in the risk assessment

Table IIIA 7.3.2.2-3 Raw PHED exposure estimates based on "best Fit" [b] statistical measure

Ground boom application	mg as / kg as handled ("best fit")						
	Dermal Body	Dermal Hands	Dermal Total	Dermal Absorbed[a]	Inhalation	Inhalation + Dermal Total [c]	Inhalation + Dermal Absorbed
PHED mixer / loader file	284.6	43	327.6	327.6	3.4	331	331
PHED applicator file	37.2	28.8	66	66	3.2	69.2	69.2
PHED mixer / loader / applicator file	321.8	71.8	393.6	393.6	6.6	400.2	400.2

[a] total dermal dose x percentage dermal absorption (default value of 100 % used)

[b] "best fit" estimate based on adding arithmetic means for normal distributions, geometric means for lognormal distributions and medians for other distributions.

[c] dermal absorption data should not be used if a dermal toxicity value is used in the risk assessment

Table IIIA 7.3.2.2-4 Scenario specific exposure estimates based on arithmetic means

Worker exposure scenario	PHED unit exposure (mg as/kg as handled)			Exposure pattern	Daily dose (mg as/kg bw/d)		
	Dermal (specify if absorbed) [b, c]	Inhalation	Total		Dermal Absorbed [a]	Inhalation	Total
Farmer – mixer / loader	914	5	919	Application to 440 ha at 20 g -as/ha	114.9	0.6	115.5
Farmer – applicator	285.4	8.6	294		35.9	1.1	37.0
Farmer – mixer / loader / applicator	1,199.4	13.6	1,213		150.8	1.7	152.5
Custom – mixer / loader	914	5	919	Application to 2,700 ha at 20 g as/ha	705.1	3.9	708.9
Custom – applicator	285.4	8.6	294		220.2	6.6	226.8
Custom – mixer / loader / applicator	1,199.4	13.6	1,213		925.3	10.5	935.7

[a] calculated as mg as/kg as handled x application rate / area x area treated / body weight (kg)

[b] reference dermal absorption template or default value - default value of 100 %

[c] dermal absorption data should not be used if a dermal toxicity value is used in the risk assessment.

Table IIIA 7.3.2.2-5 Scenario specific exposure estimates based on best fit statistical measure

Worker exposure scenario	PHED unit exposure (mg as/kg as handled)			Exposure pattern	Daily dose (mg as/kg bw/d)		
	Dermal (specify if absorbed) [b, c]	Inhalation	Total		Dermal Absorbed [a]	Inhalation	Total
Farmer – mixer / loader	327.6	3.4	331	Application to 440 ha at 20 g –as/ha	41.2	0.4	41.6
Farmer – applicator	66	3.2	69.2		8.3	0.4	8.7
Farmer – mixer / loader / applicator	393.6	6.6	400.2		49.5	0.8	50.3
Custom – mixer / loader	327.6	3.4	331	Application to 2,700 ha at 20 g as/ha	252.7	2.62	255.3
Custom – applicator	66	3.2	69.2		50.9	2.5	53.4
Custom – mixer / loader / applicator	393.6	6.6	400.2		303.6	5.12	308.7

[a] calculated as mg as/kg as handled x application rate / area x area treated / body weight (kg)

[b] reference dermal absorption template or default value - default value of 100 %

[c] dermal absorption data should not be used if a dermal toxicity value is used in the risk assessment.

Limitations

PHED provides an adequate basis for estimating occupational exposure for the proposed use of OEC 2222. However, PHED does not include data to permit estimation of exposure during clean-up or repair activities. Exposure potentially encountered during these activities is not included in the estimate reported.

It is not possible to quantify the variability of the PHED exposure estimates.

CONCLUSIONS

A "best-fit" exposure of 50.3 µg as/kg-bw/day was estimated for farmers mixing, loading and applying 20 g as/ha to treat 440 ha using ground boom equipment. The estimate is based on total dermal deposition and 100 % dermal absorption. The primary route of exposure was dermal, only 1.6 % being by inhalation

A "best-fit" exposure of 308.7 µg as/kg-bw/day was estimated for custom (contract) applicators, mixing, loading and applying 20 g as/ha to treat 2,700 ha using ground boom equipment. The estimate reported is probably an overestimate as it is often different individuals mix and load product to those that apply product. In addition, high capacity ground-boom rigs are usually "closed cab".

The estimated operator exposure values obtained are summarized in Table IIA 7.3.2.2-6. The estimated MOE values, obtained (x,xxx to xx,xxx) were in all cases greater than the minimum value considered acceptable (100). The minimum MOE value for chemx considered acceptable 100 and is based on the sub-chronic NOEL established in the 90-day and 1-year oral dog studies (xxx mg/kg/day).

Table IIIA 7.3.2.2-6 Estimations of operator exposure related to the MOE

Operator Exposure Scenario		Daily exposure (dermal + inhalation) 70 kg Operator Exposure mg/kg bw per day	Margin of Exposure
Application at 20 g as/ha Mixer / loaders wearing long pants, long sleeved shirts and gloves Applicators wearing long pants, long sleeved shirts and no gloves	Farmer: Mixer / loader / applicator treating 440 ha	50.3	x,xxx [a]
	Custom applicator: Mixer / loader / applicator treating 2,700 ha	308.7	xxx [a]

[a] based on the NOEL established in the 90-day and one year dog dietary studies - xxx mg/kg bw/day

(Seacombe H 1996c)

IIIA 7.3.3 Measurement of operator exposure

A study to measure operator exposure under practical conditions of use was not conducted since the estimates of exposure made using worst case assumptions, demonstrated that there is an acceptable margin of safety between the estimated exposure levels and the AOEL.

IIIA 7.4.1 Estimation of bystander exposure, assuming personal protective equipment is not used

Due to the low vapour pressure and inhalation toxicity of chemx, exposure of bystanders by the inhalation route is not anticipated. Dermal exposure due to drift of spray solution is likely to be less than 1 % of that calculated for operators using the German and UK models and therefore likely to be less than 1 % of the AOEL.

The conditions of usage of OEC 2222 as proposed pose no risk for possible spectators.

IIIA 7.4.2 Measurement of bystander exposure

A study to measure operator exposure under practical conditions of use was not conducted since the estimates of exposure made using worst case assumptions, demonstrated that there is an acceptable margin of safety between the estimated exposure levels and the AOEL.

IIIA 7.5.1 Estimation of worker exposure, assuming personal protective equipment is not used

It is not proposed that OEC 2222 be used at times when it is necessary to enter treated areas shortly after application. It is therefore not necessary to determine a particular re-entry time for workers or to provide an estimate of the level of worker exposure.

IIIA 7.5.2 Estimation of worker exposure, assuming personal protective equipment is used

It is not proposed that OEC 2222 be used at times when it is necessary to enter treated areas shortly after application. It is therefore not necessary to determine a particular re-entry time for workers or to provide an estimate of the level of worker exposure. It is good husbandry practice not to enter treated fields until the plants are dry, without wearing protective clothing similar to that used in application of the product.

IIIA 7.5.3 Estimation of worker exposure, assuming personal protective equipment is used and using data generated on dislogeable residues under the proposed conditions of use

It is not proposed that OEC 2222 be used at times when it is necessary to enter treated areas shortly after application. It is therefore not necessary to determine a particular re-entry time for workers, to generate data on dislogeable residues (see point IIIA 7.7), or to provide an estimate of the level of worker exposure.

IIIA 7.5.4 Measurement of worker exposure

A study to measure worker exposure under practical conditions of use was not conducted since workers will not be required to enter treated crops shortly after application.

IIIA 7.6 Dermal absorption, *in vivo*, in the rat

Dermal absorption studies were judged to be not necessary because of -

i the absence of toxicity following dermal application of chemx for 28 days in rats leading to a 'no-observable-effect' level of xxxx mg/kg body weight/day, and

ii the low level of operator exposure likely to occur.

IIIA 7.7 Dislodgeable residues

Studies to determine levels of dislodgeable residues were judged to be not necessary because of the fact that workers will not be required to enter treated crops shortly after application.

IIIA 7.8 Epidemiology

Since OEC 2222 is a new plant protection product containing the new active substance chemx, epidemiological data does not yet exist.

IIIA 7.9.1 Material safety data sheet for each formulant

Copies have been provided (Document H).

IIIA 7.9.2 Available toxicological data for each formulant

Additional data is not currently available to the applicant.

IIIA 7.10 **Domestic animal / livestock safety**

Since residues in treated produce likely to be used in feedingstuffs or in pet food will not exceed the LOQ for chemx, dietary exposure will be insignificant.

Exposure of domestic pets as a result of entering treated crops, even if entry is effected during or immediately following application, is unlikely to result in

IIIA 7.11 **Other / special studies**

None were deemed necessary.