

APPENDIX 10

FORMAT FOR THE COMPILATION OF *TIER III* OVERALL SUMMARIES AND ASSESSMENTS

The example of a summary and overall assessment which follows is intended to illustrate the approach recommended for the preparation of *Tier III* overall 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.

Chapter 1 The active substance, its properties, uses, proposed classification and labelling

1.1 Identity of the active substance and preparations containing it

All relevant information and data concerning the identity of chemx and of the formulated product OEC 2222 have been provided in the relevant *Tier II* summaries (Section 1) except in the case of confidential information which is included in Document J.

1.2 Physical and chemical properties

Chemx is a sulfonyl urea herbicide. A full specification for chemx as manufactured is included in Document J. It is a white odourless solid with a minimum level of purity of 98 %. It has no adverse physical and chemical properties. It has a melting point of 201.1 - 201.7 °C and has a low vapour pressure. It is a moderately polar molecule being relatively insoluble in non-polar solvents (*circa* 1 mg/kg in hexane) and is moderately solubility in water and other polar solvents. Since the octanol/water partition co-efficient of chemx is less than 1, bioaccumulation of chemx in environmental samples is considered unlikely. Chemx is stable to hydrolysis under neutral and basic conditions ($t_{1/2}$ of 168 and 156 d respectively), but is more readily hydrolysed under acidic conditions ($t_{1/2}$ of 48 d at pH 5 and $t_{1/2}$ of 7 d at pH 4). Chemx degrades photolytically ($t_{1/2}$ of 3 d). Photolysis is likely to be a significant pathway for degradation of chemx in the environmental.

OEC 2222 is a water dispersible granule (WG) containing 816 g/kg technical grade chemx (800 g/kg pure chemx). It is not explosive, oxidizing or flammable. Its stability as indicated by accelerated storage testing, is expected to be satisfactory - 2-year ambient temperature testing is underway.

1.3 Details of uses and further information.

OEC 2222 is a contact and residual acting herbicide for use in wheat. It is recommended as a spring post-emergence treatment to control a number of weeds including *Agropyron repens*, *Bromus sp.*, *Galium Aparine*, and various other broad leafed weeds, using ground equipment only. The maximum application rate is 25 g of product per hectare equivalent to 20 g as/ha. It is to be applied once per growing season at GS 13 - 39. It will be marketed in x kg foil lined bags. Under conditions prevailing in most European countries, farmers would

typically treat 50 ha per day, while under North American conditions, farmers would typically treat 100 ha per day.

1.4 **Classification and labelling**

1.4.1 **Classification and labelling of Chemx**

Physical and chemical properties:	No classification
Toxicological data:	No classification
Environmental fate and behaviour data:	No classification
Environmental effects:	No classification

On the basis of that classification, the proposed label for chemx is as follows:

Symbol:	None
Indication of Danger:	None
Risk phrases:	Very toxic to aquatic organisms Toxic to flora
Safety Phrase	Keep out of the reach of children Avoid release to the environment. Refer to special instructions / Safety data sheets

1.4.2 **Classification and labelling of OEC 2222**

Physical and chemical properties:	No classification.
Toxicological data:	No classification
Environmental fate and behaviour data:	No classification
Environmental effects:	No classification

On the basis of that classification, the proposed label for OEC 2222 is as follows:

Symbol:	None
Indication of danger:	None
Risk phrases:	Toxic to algae and aquatic plants
Safety phrases:	Keep out of reach of children Do not re-use container for any other purpose and dispose of safely Do not contaminate ponds, waterways or ditches with chemical or used container

Chapter 2 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

A HPLC method for the analysis of the active substance in technical grade chemx is proposed. The method has been shown to have satisfactory specificity, linearity, accuracy and repeatability.

The specificity, linearity, accuracy and repeatability of the series of methods proposed for analysis of significant impurities in the active substance (content ≥ 1 g/kg) as manufactured, are being determined and will be submitted when the report becomes available.

2.2 Methods for formulation analysis

A HPLC method for the analysis of the preparation is proposed. The method has been shown to have satisfactory specificity, linearity, accuracy and repeatability.

Existing CIPAC methods are not suitable for the analysis of chemx.

2.3 Methods for residue analysis

2.3.1 Multi-residue methods for residue analysis

The following multi-residue methods were not suitable for the analysis of chemx residues -

S8 and S19 Deutsche Forschungsgemeinschaft

Multi-residue method No. 5, Dutch "Analytical methods for residues in pesticides"

2.3.2 Methods for residue analysis of plants and plant products

The residue of concern was defined on the basis of the wheat metabolism study as **“the sum of chemx and its ethylsulfone metabolites, expressed as chemx”**.

The HPLC common moiety method of analysis proposed for wheat, determines residues of parent chemx and its metabolites, which can be hydrolysed to the metabolite 7 target analyte. The method has been shown to provide satisfactory recoveries (73 – 104 %) for the analysis of grain, straw and forage and has a limit of quantification of 0.01 mg/kg. On analysis of control samples of grain, straw and forage, the chromatograms generated showed no interferences from wheat components or from reagents, solvents and glassware used. Spiked samples gave doublets and in some instances, the peak was not well defined. Good linearity ($r=0.9999$) was observed in the range of 0.0025-0.1 $\mu\text{g/mL}$ for the target analyte (external reference standard). The standard deviations of the recoveries determined following spiking at the limit of quantification provided evidence that the method has satisfactory repeatability. The inter-laboratory validation study conducted demonstrated satisfactory reproducibility.

Endogenous method validation with ^{14}C -chemx pre- and post-emergence treated wheat forage, straw and grain (Chem2 label containing incurred ^{14}C -residues) from the wheat metabolism study was conducted to verify the conversion of chemx and its chem2-containing metabolites to metabolite 7. In the wheat metabolism studies using chemx labelled in the chem2 moiety, it was demonstrated that identified chem2 containing metabolites and chemx represented 80 % and 60 % of the total residue in forage and straw, respectively. The residue levels

present in grain were too low for accurate quantification. As the efficiency of the method was very good for the more complex straw and forage matrices, it is expected to be satisfactory for the grain matrix. The identity of metabolite 7, resulting from acid hydrolysis of chemx residues, was confirmed with mass spectral data.

Residues were calculated as mg/kg metabolite 7 and were expressed in terms of chemx parent equivalent. A limit of quantification of 0.01 mg/kg for metabolite 7, expressed as chemx equivalent, can be achieved. In the light of the complexity of the method, it is proposed that the limit of quantification be specified, for control purposes, as being 0.02 mg/kg. Use of the method results in residue content of parent chemx being over estimated by between 10 and 20 %.

2.3.3 Methods for residue analysis of food of animal origin

A HPLC common moiety method for the determination of residues of chemx, and its metabolites that can be hydrolysed to metabolite 7, in food of animal origin is proposed. The method was found to give satisfactory recoveries for the analysis of milk, meat, fat, liver and kidney and has a limit of quantification of 0.003 mg/kg in the case of milk and 0.005 mg/kg for meat, fat, liver and kidney. The method was found to have satisfactory linearity, specificity and repeatability. Representative chromatograms generated through analysis of control samples of milk and liver showed that there was no background interference. On analysis, spiked samples had well resolved peaks of metabolite 7 with no associated interference. The detector response was linear in the range 0.01 to 0.35 mg/kg.

An independent laboratory validation demonstrated the reliability and reproducibility of the method for the determination of chemx in milk, fat, kidney, liver and muscle samples. Whole milk and liver were selected to represent the range of livestock matrices.

Endogenous method validation with ¹⁴C-chemx was conducted using milk and liver samples from the goat metabolism study. In addition, an exogenous method validation study with ¹⁴C-chemx was carried out using control samples of milk and tissue samples spiked with chem2-labelled ¹⁴C-chemx. The results of these studies demonstrated that chem2-containing residues accounted for 80 to 85 % of the total residue in milk and liver samples. There was good repeatability between replicates. The recoveries obtained were more than 71 % in the case of milk and more than 85 % in the case of liver samples. Extraction efficiencies for endogenous chem2 containing residues in milk and liver were 92 and 101 %, respectively, which were comparable to those obtained in the goat metabolism study (95 % in milk, 104 % in liver).

The results of the rat metabolism study (point IIA 5.1/01, Smith, H 1996) confirmed that parent chemx corresponded to > 80 % of the excreted dose.

2.3.4 Methods for residue analysis of soil

Three different methods were provided for the analysis of residues in soil. The methods concerned determine residues of -

parent chemx only,

parent chemx and its metabolite 2 metabolite, as metabolite 7, obtained by acid hydrolysis

parent chemx and its metabolite 1 and metabolite 2 metabolites as metabolite 7, obtained by acid hydrolysis.

All three methods of analysis have been validated for analysis of chemx residues in soil (recovery, linearity, specificity, limit of quantification and repeatability). Work is on-going with respect to the validation of the

Chemco	September 1997	Chemx (proposed ISO name)	page of
--------	----------------	---------------------------	---------

methods for determination of metabolite 1 and metabolite 2 residues. As soon as it becomes available the report generated will be submitted.

2.3.5 **Methods for residue analysis of water**

The HPLC method provided for the analysis of residues in water, involves quantitative conversion of chemx and its metabolite 2 metabolite to metabolite 7 by means of acid hydrolysis. Residues are calculated as mg/kg metabolite 7 and are expressed in terms of chemx parent equivalent.

The method which was shown to have a limit of quantification of 0.1 µg/L has been validated (recovery, linearity, specificity and repeatability) with respect to parent chemx residues. Work is on-going with respect to the validation of the method for determination of metabolite 2 residues. As soon as it becomes available the report generated will be submitted.

2.3.6 **Methods for residue analysis of air**

On the basis of chemx's vapour pressure and Henry's Law constant, it is clear that it is quite unlikely that chemx would be found in air. Consequently, exposure of operators, workers and bystanders by the inhalation route will be minimal. It is therefore contended that an analytical method for air is not required. However as analysis of air was conducted in the context of rat inhalation study, details of the methodology were provided below (point IIA 4.7). As it is claimed that such an analytical method is not required, not all of the usual parameters were reported.

The HPLC method provided can be used to measure concentrations in air at levels of 2.8 mg/L. Work is on-going with respect to the validation of the method. As soon as it becomes available the report generated will be submitted.

Chapter 3 Impact on human and animal health

3.1 Effects having relevance to human and animal health arising from exposure to the active substance or to impurities in the active substance or to their transformation products

3.1.1 Absorption, distribution, metabolism and excretion

In a metabolism study 2 forms of chemx (98% purity), labelled with ¹⁴C at the C-3 or C-5 positions of the chem2 ring were administered to 4 Sprague-Dawley rats/sex/dose in multiple doses by oral gavage or intravenous injection at dose levels of 0, x1, x2, x3 mg/kg bw/day.

Chemx and its metabolites were readily excreted by the rat with urinary excretion being the major route of elimination (77 - 87 % vs 4.77 - 13.2 % in faeces) for all animals receiving a low dose, and faecal excretion being the predominant route of elimination (approximately 59 % vs 31.8 - 33.4% in urine) following administration of the high dose. Expiration as carbon dioxide or other volatile compounds was not a significant route of elimination (< 0.04 % radioactivity recovered as CO₂ after 24 h). In the low dose groups, absorption was greater than 90 % while at the high dose, absorption averaged approximately 40 %. There was little evidence of retention of chemx or its metabolites - tissue and blood levels were negligible and apart from the liver (< 0.13%), no individual tissue contained more than 0.01 % of the administered dose. Greater than 90 % of the administered dose was excreted three days after administration. The major component of the excreted radioactivity was unchanged chemx.

Metabolism of chemx in the rat occurred to a limited extent *via* demethylation and chem2 ring hydroxylation. The cleavage of the xxx bond of chemx to form separate chem2 and chem3 metabolites is a minor metabolic pathway in the rat. There was little difference in the metabolic profile regardless of the route of administration, dose level or sex. Some slight quantitative differences in minor metabolites were seen between the sexes. Repeated dosing did not affect the metabolic profile. The pathways identified/postulated for the metabolism of chemx in animals are outlined in Figure 3.1-1. For comparative purposes, the pathways in plants, soil and water, are also included.

Figure 3.1-1 Proposed pathways for metabolism of chemx in rats, wheat, soil and water

Pathway omitted

3.1.2 Acute toxicity

Chemx was found to be of a low order of acute toxicity following exposure *via* oral (gavage), dermal and inhalation routes of administration. Chemx was found to be non-irritating to rabbit skin and caused moderate, reversible ocular irritation. The formulated product (OEC 2222) caused slight, reversible ocular irritation. Both chemx and OEC 2222 were found to be non-sensitising to the guinea pig in maximisation assays.

Table 3.1-1 Summary of the acute toxicity of chemx

Type of study	Species	Results	
		Active substance	OEC 2222
Oral route	Rat	LD ₅₀ > 5000 mg/kg	LD ₅₀ > xxxx mg as/kg
Dermal route	Rat	LD ₅₀ > 5000 mg/kg	LD ₅₀ > xxxx mg as/kg
Inhalation	Rat	LC ₅₀ at 4 hours > 3.0 mg/L	LC ₅₀ at 4 hours > xx mg as/L
Primary skin irritation	Rabbit	Non-irritating	Non-irritating
Eye irritation	Rabbit	Moderately irritating	Slightly irritating
Skin sensitisation	Guinea pig	Not sensitising	Not sensitising

3.1.3 Genotoxicity

Chemx was tested for its genotoxic potential using the usual battery of *in vitro* (bacterial assay for gene mutation, clastogenicity in mammalian cells, and gene mutation in mammalian cells) and *in vivo* (mouse bone marrow micronucleus assay) tests. All test results were negative.

Table 3.1-2 Summary of the genotoxicity studies with chemx

Assay	Species / Cell Type / strain	Doses	Finding	Comment
Bacterial assay for gene mutation	<i>S. typhimurium</i> (strains TA98, TA100, TA102, TA1535, TA1537)	5, 15, 50, 150, 1500 and x,xxx µg/plate	negative ± metabolic activation	Sensitivity demonstrated - positive control
Clastogenicity in mammalian cells	Human lymphocytes	100, 250, 500, 750 and x,xxx µg/mL	negative ± metabolic activation	Sensitivity demonstrated - positive control
Gene mutation in mammalian cells	Chinese hamster ovary (CHO) cells	Initial trial: 624, 1,250, 2,500 and x,xxx µ/mL Confirmatory trial: 312, 624, 1,250, 2,500 and x,xxx µg/mL	negative ± metabolic activation	Sensitivity demonstrated - positive control

Assay	Species / Cell Type / strain	Doses	Finding	Comment
Mouse bone marrow micronucleus assay	Mouse: Charles River CD-1	0, 1,250, 2,500 and x,xxx mg/kg bw	Negative	Sensitivity demonstrated - positive control
Mouse bone marrow micronucleus assay	Mouse: Charles River CD-1	x,xxx mg/kg bw	Negative	Presence of radioactivity confirmed exposure of marrow cells

3.1.4 Sub-chronic and chronic toxicity

The sub-chronic and chronic toxicity of chemx was investigated in mice, rats and dogs. A series of oral range-finding 28-day studies were conducted initially. These were used to establish appropriate dose levels to be used in the 90-day studies, which in turn were used to establish appropriate dose levels to be used in the long-term studies.

3.1.4.1 Sub-chronic and chronic toxicity in the mouse

In a mouse range-finding study, doses of 0, 10, 100, 1,000 and x,000 mg/kg in the diet (0, 10, 100, 1,000 and x,000 ppm) (mean achieved dose 2.0, 17, 186 and x01 mg/kg bw/day in males and 2.7, 22, 274 and xx7 mg/kg bw/day in females) were administered in the feed or four weeks. The only findings were in the high dose males and consisted of slight reduction in mean weight gain, a single ocular opacity and slightly induced palmitoyl CoA activity. The NOAEL for males was xxx mg/kg bw/day and for females was xxx mg/kg bw/day.

Chemx was given for 90 days to groups of 20 CD-1 mice at concentrations of 0, 100, 1,000, 3,000 and x,000 mg/kg in the diet (0, 100, 1,000, 3,000 and x,000 ppm) (mean achieved dose 18, 163, 550 and x,xxx mg/kg bw/day in males and 32, 313, 887 and x,xxx mg/kg bw/day in females). The only possibly treatment-related effect was an equivocal decrease in ALP in high dose animals. The NOAEL for the study was set at x,000 ppm (xxx mg/kg bw/day for males and xxx bw/day for females), since there were no treatment-related effects at up to and including the highest dose.

In a carcinogenicity study, CD-1 mice were fed diets containing chemx at target concentrations of 0, 30, 700, 3,000 and x,000 mg/kg in the diet (0, 30, 700, 3,000 and x,000 ppm) for 18 months (mean achieved dose 4, 93, 394 and x,xxx mg/kg bw/day in males and 6.5, 153, 635 and x,xxx mg/kg bw/day in females). A number of clinical signs were noted among the high dose males that were considered related to urinary calculi. An increase in body weight gain and in food consumption was noted at intervals during the study. Although possibly treatment-related, this was not considered to be biologically relevant. Statistically significant increases in platelet count in high dose females at interim and terminal sacrifices were considered treatment-related. A number of altered haematological parameters were not considered to be of biological significance or were not judged to be treatment-related due to a lack of consistency between interim and terminal sacrifice values. A dose-related increase (statistically significant at the high dose) in BUN was noted in males at termination. A similar trend occurred in females. Other alterations in clinical chemistry parameters were not considered to be biologically relevant.

Evidence of bladder and kidney injury was found at pathological examination. An increased incidence of mesenchymal tumours of the urinary bladder in males at the two highest doses was considered related to the

presence of calculi and hyperplasia of the transitional cell epithelium. On the basis of the renal and bladder lesions associated with urinary calculi which occurred at 3,000 ppm and above in males the NOEL for neoplastic and non-neoplastic change was xxx mg/kg diet (xx mg/kg bw/day).

3.1.4.2 Sub-chronic and chronic toxicity in the rat

In a range-finding study, chemx was administered to rats for 28 days at levels of 20, 200, 2,000 and x,000 mg/kg in the diet (20, 200, 2,000 and x,000 ppm) (mean achieved dose 1.3, 13.7, 136.5 and xxx.x mg/kg bw/day in males and 1.5, 15.6, 154.1 and xxx.x mg/kg bw/day in females). The only findings considered related to be treatment related occurred at the high dose (xxx mg/kg bw/day in males and xxx mg/kg bw/day in females). A slight decrease in activated partial thromboplastin time was noted in the high dose females. In addition slight kidney effects (protein accumulation in renal tubular epithelia) which may have been treatment related were seen in both sexes at the high dose. The NOAEL for the study was x,xxx mg/kg feed (highest dose tested) since at that dose there were no toxicologically significant treatment related effects in either male or female rates (NOAEL = xxx mg/kg bw/day in males and xxx mg/kg bw/day in females).

In a 90-day study, chemx was administered to groups of 30 Sprague-Dawley rats (10 males and 20 females) at concentrations of 0, 20, 200, 2,000, 6,000 and xx,000 mg/kg in the diet (0, 20, 200, 2,000, 6,000 and xx,000 ppm) (mean achieved dose 1.2, 12.1, 123.2, 370 and x,xxx mg/kg bw/day in males and 1.5, 14.6, 144.3, 448 and x,xxx mg/kg bw/day in females). The study included a preliminary reproductive toxicity test (10 females per group). Dietary exposure to chemx resulted in slight body weight effects in males at the high dose and in pregnant females. Slight alterations to haematological parameters in high dose females may have been treatment-related. A number of lesions were identified in the kidneys, ureters and bladders of a number of high dose males and females. On the basis of the toxicological profile of chemx determined in other studies reported, it is concluded that the renal and bladder effects seen in this study at the high dose were treatment-related. The NOAEL was xxx mg/kg bw/day for males and xxx mg/kg bw/day for females) based on body weight reduction in males at the next highest dose and bladder effects observed at the next highest dose tested in both males (xxx mg/kg bw/day) and females (xxx mg/kg bw/day).

In a combined chronic toxicity and carcinogenicity study, CD rats were administered diets containing chemx at target concentrations of 0, 50, 500, 5,000, and xx,000 mg/kg diet (0, 50, 500, 5,000, and xx,000 ppm) for up to 22 months (mean achieved dose 2.4, 24.4, 244 and x,xxx mg/kg bw/day in males and 3.1, 30.4, 314.1 and x,xxx mg/kg bw/day in females). Treatment resulted in significantly increased mortality for males in the xx,000 mg/kg group. All of the deaths resulted from urinary calculi and related abnormalities in the kidneys, urinary bladder and ureters. In addition, a slight increase in mortality rate was noted for females in the xx,000 mg/kg group, which was also associated with an increased incidence of urinary calculi and related abnormalities. Although the effect was less pronounced than for males, and did not necessitate early sacrifice of the xx,000 mg/kg group females, it may nevertheless have been treatment related.

The only treatment-related clinical observation was an increased incidence of blood-like urine colour in the xx,000 mg/kg males. Treatment with chemx also resulted in slightly lower mean body weight gain in the xx,000 mg/kg group, in both sexes.

At necropsy, treatment-related findings were observed in the kidneys (calculi, pelvic dilatation), urinary bladder (calculi, thickened mucosa) and ureters (calculi, dilatation) in the xx,000 mg/kg group, both sexes, and in the 5,000 mg/kg group, females only. In addition, an increased incidence of enlarged parathyroids and emaciation were observed in xx,000 mg/kg females.

The results of the histopathological examinations conducted supported the findings noted at gross necropsy. In the kidneys, treatment-related findings were: pelvic epithelial hyperplasia and pelvic dilatation (xx,000 mg/kg

group, both sexes, 5,000 mg/kg group, females only); calculi (5,000 and xx,000 mg/kg groups, both sexes); squamous metaplasia and pyelonephritis (xx,000 mg/kg group, females only); mineralization in the cortex and medulla (xx,000 mg/kg group, both sexes, 5,000 mg/kg group, males only); and papillary necrosis (xx,000 mg/kg group, males only). In the urinary bladder, treatment-related findings were: calculi (xx,000 mg/kg group, males only); mucosal epithelial hyperplasia (xx,000 mg/kg group, both sexes - a slight increase noted at 5,000 mg/kg in males only was considered to possibly be treatment related); and haemorrhage (5,000 and xx,000 mg/kg groups, males only). Treatment-related findings observed in the ureters were noted in the xx,000 mg/kg group, both sexes, included dilatation, mucosal epithelial hyperplasia, erosion/ulceration, amorphous debris (males only) and squamous metaplasia (females only). Mineralization of various tissues (*e.g.* aorta, heart, lung, muscle) was observed in the xx,000 mg/kg group, females only (these tissues were not examined in xx,000 mg/kg males) and in the 5,000 mg/kg group, males only. In addition, an increased incidence of parathyroid hyperplasia and fibrous osteodystrophy were noted for females in the xx,000 mg/kg group.

Urinalysis revealed an increased incidence of unidentifiable and/or abnormal crystal types in the 5,000 and xx,000 mg/kg groups, both sexes.

A slight increase in mean blood urea nitrogen, sodium and chloride values observed in the 5,000 and xx,000 mg/kg female groups only, was considered to be treatment-related.

A single papilloma and a single transitional cell carcinoma were observed in the urinary bladder of 2 different females in the 5,000 mg/kg group. Both affected females also had calculi in the urinary bladder. Although bladder tumours were not observed in any of the females in the xx,000 mg/kg group, it is known that calculi can elicit hyperplasia and neoplasia resulting from direct irritation of the bladder epithelium. Accordingly, the 2 tumours observed in the 5,000 mg/kg group were considered to possibly be treatment related.

The NOEL for systemic toxicity and tumorigenicity was xx.x mg/kg bw/day for males and xx.x mg/kg bw/day for females and is based on treatment-related effects to the urinary system at dose levels of 5,000 and xx,000 mg/kg. All results were negative following both *in vitro* and *in vivo* testing of chemx for its genotoxic potential. It was therefore concluded that the tumourigenicity observed was due to an epigenetic mechanism *i.e.* direct epithelial irritation. There were no other tumours related to treatment with chemx.

There was no evidence of treatment related toxicological effects in the rat following dermal exposure for 28 days to 100, 300 or x,000 mg/kg bw/day chemx.

3.1.4.3 Sub-chronic toxicity in the dog

In a dog range-finding test, doses of 30, 100, 300 and x,000 mg/kg bw/day were given neat in gelatine capsules daily, 5 days/week, for 4 weeks to 2 dogs/sex/dose. The only findings considered possibly related to treatment were a slightly reduced weight gain in females at the two highest doses and elevated ALP and CPK in high dose males. The no-observed-adverse-effect level (NOAEL) was xxx mg/kg bw/day in females and xxx mg/kg bw/day in males.

In a 90-day study, groups of 5 beagle dogs/sex/dose were administered chemx in gelatine capsules at doses of 0, 30, 100, 300 and x,000 mg/kg bw/day, 5 days/week, for 90 days. The urinary tract was identified as the target organ. The pattern of response was somewhat unusual in that there was a low incidence of findings at ≥ 300 mg/kg bw/day but in one male animal the effect was very severe, necessitating premature termination. The entire urinary tract was targeted in this animal while only the bladder showed evidence of substance-related damage in the others. These findings are consistent with irritation caused by crystals in the urine and damage following the formation of calculi. Urinary crystals were identified previously in the ADME study (point IIA

5.1.1 to 5.1.3) and were identified in this study at the interim (males and females) and termination (females only) sampling. The NOEL was xxx mg/kg bw/day for females and xxx mg/kg bw/day for males.

Five groups of 5 male and 5 female beagle dogs were dosed with gelatine capsules containing doses of 0, 5, 20, 100 and x00 mg/kg bw/day, 5 days/week, for one year. A single high dose animal was affected by treatment. Increased levels of AST and ALT were recorded. There was no macroscopic or microscopic evidence of liver damage or of damage to other tissues, other than pathological evidence of an adverse effect on the bladder of the single high dose animal affected. It was concluded that the bladder mucosa pathology resulted from the irritant action of the calculus and was not as a result of direct action by the test material on the bladder cells. The NOEL for the study was xxx mg/kg bw/day in both males and females.

3.1.4.4 Reproductive and developmental toxicity

A two-generation reproductive toxicity study was carried out in the rat. Diets containing target levels of 0, 50, 500, 5,000 and xx,000 mg/kg (0, 50, 500, 5,000 and xx,000 ppm) were prepared and fed to 30/sex CD (SD) rats for 10 weeks prior to mating of the first generation and throughout the second generation (mean achieved F₀ dose 3.1, 31.6, 312 and x,xxx mg/kg bw/day in males and 3.6, 36.2, 363.2 and x,xxx mg/kg bw/day in females, mean achieved F_{1A} dose 3.1, 31.1, 315.8 and x,xxx mg/kg bw/day in males and 3.7, 37.1, 377.8 and x,xxx mg/kg bw/day in females). An additional mating trial was carried out to investigate the lack of copulatory activity in the high dose F₀ males.

Treatment-related effects on body weight and/or body weight gain were observed at the high dose in the F₀ and F_{1A} parental females at various intervals. Reproductive parameters were not adversely affected. A reduction in copulatory activity in some (10) high dose F₀ males was further investigated in a second mating which resulted in normal performance. One of the ten males died during the mating trial of possibly urinary calculus-related causes before the second mating trial. The authors suggested that this condition could have an adverse effect on mating behaviour. No other explanation was offered for the lack of normal behaviour in the first mating, but as these males subsequently performed normally, it is not considered to be treatment-related. There was no effect on copulatory behaviour in the second generation. A statistically significant decrease in the numbers of pregnant females/total paired and pregnant/confirmed copulation was observed when compared to the controls. The authors of the study report attributed this observation to the unusually high values obtained in the controls. This observation was confirmed on review of historical control data.

A possible reduction in post-natal survival to day 4 was observed in the F_{1A} litters at the highest dose level, but not in the F_{2A} litters at the highest dose level.

There was some pathological evidence of the targeting of the urinary system: slightly increased relative renal weights at the high dose level; treatment-related increases in urinary tract lesions; and small increases in renal lesions. Increases in relative and/or absolute liver weights seen in both generations were considered to be related to decreased body weights and not were not considered to be treatment-related effects, because of the lack of correlation with increasing dose and the absence of histological changes. The increased incidence of accentuated lobular pattern in the F₀ males was not considered to be of biological relevance. The NOEL for the study was xxx mg/kg bw/day in males and xxx mg/kg bw/day in females).

In a developmental toxicity study in rats, doses of 0, 100, 300 and x,000 mg/kg bw/day were given daily by gavage to 25/dose CD@(SD)BR on gestation days 6 to 15. Neither maternal health nor intrauterine growth or development of the rat foetus were adversely affected. Some malformations were observed. There was no treatment-related trend in either the incidence or type of anomalies observed. The incidence of skeletal variations was similar in control and treated groups. The NOEL for systemic toxicity and for developmental toxicity was greater than the highest dose tested.

Appendix 10 Format for the Compilation of *Tier III* Overall Summaries and Assessments

Chemco	September 1997	Chemx (proposed ISO name)	page of
--------	----------------	---------------------------	---------

Daily gavage doses of 0, 50, 250 and x,000 mg/kg bw/day were given daily NZW rabbits (20 / group) on gestation days 7 to 19. There were no treatment-related toxicological effects on pregnant dams administered up to x,000 mg/kg bw/day. There was no evidence of developmental toxicity at any dose level. The NOEL for the study was x,000 mg/kg bw/day for maternal and developmental toxicity, based on a lack of effects at the highest dose tested .

Table 3.1-3 Summary of the sub-chronic and chronic toxicity studies with chemx

Type of study	Species/strain	Doses (mg/kg bw/day)	NOEL/NOAEL (mg/kg bw/day)	Comments, effects, target organs
Oral route, 28 days	CD-1 Mice	♂ 2, 17, 186 and xxx ♀ 2.7, 22, 274 and xxx	♂ xxx ♀ xxx	no toxicologically significant treatment related effects at the highest dose
Oral route, 28 days	Sprague-Dawley Rat	♂ 1.32, 13.71, 136.47 and xxx.xx ♀ 1.52, 15.64, 154.13 and xxx.xx	♂ xxx ♀ xxx	non adverse cumulative weight gain in females at the 2 highest doses
Oral route, 28 days	Beagle Dog	30, 100, 300 and xxxx	♂ xxx ♀ xxx	♀ based on bw gain at the 2 highest doses ♂ elevated alkaline phosphatase and CPK at the high dose
Oral route, 90 days	CD-1 Mice	♂ 18, 163, 550 and xxxx ♀ 32, 313, 887 and xxxx	♂ xxxx ♀ xxxx	no treatment related effects
Oral route, 90 days	Sprague-Dawley Rat	♂ 1.22, 12.1, 123.2, 370 and xxxx ♀ 1.47, 14.6, 144.3, 448 and xxxx	♂ xxx ♀ xxx	based on bw gain in high dose males and the occurrence of calculi in both sexes at the high dose
Oral route, 90 days	Beagle Dog	30, 100, 300 and xxxx	♂ xxx ♀ xxx	urinary tract gross and microscopic effects consistent with irritation at the 2 highest doses
Oral route, 1-year	Beagle Dog	5, 20, 100 and xxx	♂ xxx ♀ xxx	increased AST and ALT and urinary tract gross and microscopic effects consistent with irritation at the high dose
Cutaneous route, 28 days	CD Rats	100, 300 and xxxx	x,xxx	no treatment related effects
Oral route, 18 months	CD-1 Mice	♂ 4, 93, 394 and xxx ♀ 6.5, 153, 635 and xxxx	chronic ♀ xx ♀ xxx oncogen. ♂ xxx ♀ xxxx	clinical signs related to presence of urinary calculi in ♂ at 2 highest doses increased incidence of mesenchymal tumours of the urinary bladder in ♂ at the 2 highest doses

Type of study	Species/strain	Doses (mg/kg bw/day)	NOEL/NOAEL (mg/kg bw/day)	Comments, effects, target organs
Oral route, 22 months	CD Rats	♂ 2.4, 24.4, 244 and xxxx ♀ 3.1, 30.4, 314.1 and xxxx	chronic ♂ xx ♀ xx oncogen. ♂ xxx ♀ xx	mortalities in ♂ and ♀ at xxxx mg/kg bw/day resulted from urinary calculi and related abnormalities in 2 mid dose ♀, a papilloma and a single cell transitional cell carcinoma were observed
Multigeneration	CD Rats	F ₀ ♂ 3.1, 31.6, 312 and xxxx F ₀ ♀ 3.6, 36.2, 363.2 and xxxx F _{1A} ♂ 3.1, 31.1, 315.8 and xxxx F _{1A} ♀ 3.7, 37.1, 377.8 and xxxx	♂ xxx ♀ xxx	some evidence of targeting of the urinary system at the high dose level: slightly increased relative renal weights; treatment related increases in urinary tract lesions; and small increases in renal lesions
Teratogenicity	CD Rats	100, 300 and xxxx	> x,xxx	no adverse effect on maternal health or on intrauterine growth or development of the foetus
Teratogenicity	NZW Rabbits	50, 250 and xxxx	> x,xxx	no adverse effect on maternal health or intrauterine growth or development of the foetus

3.1.5 Neurotoxicity (acute, delayed and sub-chronic)

In an acute neurotoxicity study, chemx was administered in corn oil by gavage to four groups of 10 Sprague-Dawley rats/sex at 0, 125, 500 and x,000 mg/kg bw. There were no mortalities or treatment related changes in body weight, behavioural parameters or neuropathology. The NOEL for acute neurotoxic effects was \geq x,000 mg/kg bw.

In a sub-chronic neurotoxicity study, chemx was administered in the diet to four groups of 10 Sprague-Dawley rats/sex at target doses of 0, 200, 2,000 and xx,000 mg/kg in the diet (0, 200, 2,000 and xx,000 ppm) (mean achieved dose 14.7, 148 and xxxx mg/kg bw/day in males and 16.2, 163 and xxxx mg/kg bw/day in females). There were no mortalities. Female body weights at the low dose were significantly higher than controls for weeks 1, 5, 7 and 9. Since there was no dose response, these increases were not considered treatment related. There were no signs of neurotoxicity or systemic toxicity following dietary administration of chemx for a period of 14 weeks at doses up to xxxx to xxxx mg/kg bw/day. The NOEL for sub-chronic neurotoxic effects was \geq xxxx mg/kg bw/day.

Table 3.1-4 Summary of the acute, delayed and sub-chronic neurotoxicity studies with chemx

Type of study	Species/strain	Doses (mg/kg bw/day)	NOEL/NOAEL (mg/kg bw/day)	Comments, effects, target organs
Acute neurotoxicity, oral route	Sprague-Dawley Rat	125, 500 and xxxx	> x,xxx	no behavioural, functional or neuropathological changes occurred
Sub-chronic neurotoxicity, oral route	Sprague-Dawley Rat	♂ 14.4, 148 and x,xxx ♀ 16.2, 163 and x,xxx	> x,xxx	no signs of neurotoxicity or of systemic toxicity

3.2 Toxicological end point for assessment of risk following long-term dietary exposure (ADI)

It is proposed that the estimation of an Acceptable Daily Intake (ADI) for chemx be based on the results of the dietary chronic toxicity/carcinogenicity study in rats, the multi-generation study in rats and the carcinogenicity study in mice.

In each of these studies, the 'no-observed-effect' levels were the following:

Mouse carcinogenicity study (dietary): approximately xx mg/kg bw/day for neoplastic and non-neoplastic changes.

Rat two-year chronic toxicity study (dietary): approximately xxx and xx mg/kg bw/day in males and females, respectively, based on renal lesions observed at higher doses. Since all results were negative following both *in vitro* and *in vivo* testing of chemx for its genotoxic potential, it was concluded that the tumourigenicity observed was due to an epigenetic mechanism i.e. direct epithelial irritation by renal calculi. There were no other tumours related to treatment with chemx.

Multi-generation study in rats (dietary): approximately xxx mg/kg bw/day in males and xxx mg/kg bw/day in females, based on the presence of urinary tract microscopic changes associated with uroliths at the highest tested dose.

The lowest no-observed-effect level was in the chronic rat study at a level of xx mg/kg bw/day. Given the quality and extent of the database and the nature of the effects observed, it is proposed that a safety factor of 10 is used to take account of interspecies differences and a further factor of 10 is used to take account of intraspecies differences. For the calculation of the ADI, an overall safety factor (SF) of 100 is proposed.

The **Acceptable Daily Intake** proposed is calculated according to the following formula:

$$ADI = \frac{NOEL}{SF} = \frac{xx \text{ mg/kg/day}}{100} = 0.xx \text{ mg/kg bw/day of chemx}$$

The Maximum Acceptable Intake calculated for chemx is 0.xx mg/kg bw/day.

3.3 **Toxicological end point for assessment of risk following acute dietary exposure - ARfD (Acute reference dose)**

In the context of the low order of acute toxicity of chemx, following exposure by oral, dermal and inhalation routes, it is not necessary or appropriate to propose an acute reference dose.

3.4 **Toxicological end points for assessment of occupational and bystander risks - AOEL / MOE ²⁹**

It is proposed that the calculation of an *Acceptable Operator Exposure Level* (AOEL) or *Margin of Exposure* (MOE) value be based on the results of acute toxicity testing and toxicity following repeated exposure, in particular the results of the 28 and 90 day studies in mice, rats and dogs and the 1 year study in dogs.

Chemx was found to be of a low order of acute toxicity following exposure *via* oral (gavage), dermal and inhalation routes of administration. Chemx was found to be non-irritating to rabbit skin and caused moderate, reversible ocular irritation. The formulated product (OEC 2222) caused slight, reversible ocular irritation. Both chemx and OEC 2222 were found to be non-sensitising to the guinea pig in maximisation assays. Accordingly, the results obtained in acute toxicity testing need not be considered further for the purposes of establishing AOEL or MOE values.

Given the lack of effects in the reproductive toxicity study and the absence of developmental toxicity at any dose tested, these studies need not be considered further for the purposes of establishing AOEL or MOE values.

In the 28 and 90-day studies, the NOEL/NOAEL levels were as follows:

- | | |
|--------------------------------|---|
| Mouse 28-day study (dietary): | xxx mg/kg bw/day in males and xxx mg/kg bw/day in females, based on weight gain, ocular opacity and palmitoyl CoA activity. |
| Mouse 90-day study (dietary): | xxxx mg/kg bw/day in males and xxxx mg/kg bw/day in females, based on an equivocal decrease in alkaline phosphatase in females at the highest dose tested. |
| Rat 28-day study (dermal): | x,xxx mg/kg bw/day in males and x,xxx mg/kg bw/day in females, based on an absence of effects at the highest dose tested. |
| Rat 90-day study (dietary): | xxx mg/kg bw/day in males and xxx mg/kg bw/day in females, based on mild decrease in body weight gain in adult males and pregnant females during gestation at the highest dose and renal and bladder lesions. |
| Dog 28-day study (oral route): | xxx mg/kg bw/day in males and xxx mg/kg bw/day in females, based on reduced weight gain in females and elevated alkaline phosphatase and creatine phosphokinase in males at the highest doses. |

²⁹ The Acceptable Operator Exposure Level (AOEL) is the maximum daily dose considered to be without adverse health effect for operators, workers and by-standers. It is based on the most appropriate NOAEL from relevant studies and is the product of that value and an uncertainty factor selected on the basis of the extent and quality of the available data, the species for which data are available and the nature of the effects observed. AOEL values are used for regulatory purposes in Europe.

The Margin of Exposure (MEO) is the mathematical relationship between the level of operator exposure estimated or measured and the most appropriate NOAEL from relevant studies. The minimum MOE value necessary to ensure the health of operators, workers and by-standers, depends on the extent and quality of the available data, the species for which data are available and the nature of the effects observed. MOE values are used for regulatory purposes in North America.

Chemco	September 1997	Chemx (proposed ISO name)	page of
--------	----------------	---------------------------	---------

Dog 90-day study (oral route): xxx mg/kg bw/day in males and xxx mg/kg bw/day in females, based on urinary tract effects, associated with crystalluria and urolithiasis at the highest doses.

Dog One-year (oral route): xxx mg/kg bw/day based on bladder histopathology.

Chemx was shown to have very limited toxicity following exposure by the percutaneous route. The acute oral LD₅₀ for the rat was found to be in excess of 5,000 mg/kg bw and in the 28-day percutaneous toxicity study with rats, the NOEL was found to be x,xxx mg/kg bw/day. It is therefore appropriate to propose that the AOEL established be derived from oral toxicity studies, *i.e.* that it be a systemic AOEL.

The lowest dose not provoking any adverse effect is that used in the 90-day and in the one year dog studies - xxx mg/kg bw/day. Given the quality and extent of the database and the nature of the effects observed, it is proposed that a safety factor of 10 be used to take account of interspecies differences and that a further factor of 10 be used to take account of intraspecies differences. It is therefore proposed that a safety factor of 100 be used in calculated a systemic AOEL value.

Accordingly the AOEL proposed for chemx is x mg/kg bw/day.

In establishing the minimum MOE value for use in assessing the acceptability of estimated or actual exposure, it is necessary to have regard to the quality and extent of the data base and the nature of the effects observed. It is proposed that a safety factor of 10 be used to take account of interspecies differences and that a further factor of 10 be used to take account of intraspecies differences.

Accordingly, the minimum MEO value acceptable in comparing estimated or actual exposure with the NOEL established in the 90-day and in the one-year dog studies, is a value of 100.

3.5 Drinking water limit

No suitable human data are available and chronic exposure animal studies involving administration of chemx in drinking water were not carried out. It is therefore proposed that the Maximum Allowable Concentration (MAC) in drinking water be based on the ADI derived from dietary studies.

In order to calculate the MAC for drinking water it is appropriate to divide the ADI by an additional uncertainty factor of 10 and thus derive an allowable intake level of 0.0xx mg/kg bw/day. The International Programme on Chemical Safety (WHO, 1994) proposed that for risk assessment purposes a reference human be considered to weigh 64 kg and be considered to have a daily intake of drinking water of 1.4 litres. Thus the MAC value for chemx can be estimated as follows -

$$\text{MAC} = \frac{0.0xx \times 64 \text{ kg}}{1.4} = x.xxx \text{ mg chemx/litre} = x.xxx \text{ }\mu\text{g/L}$$

3.6 Impact on human and animal health arising from exposure to the active substance or to impurities contained in it

3.6.1 Operators – estimates relevant for Europe

The potential exposure of spray operatives to the product (OEC 2222) was estimated using the German model [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 Forstwirtschaft, Berlin, Dahlem, no. 277] and the UK model [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].

The estimated operator exposure values obtained using the German and UK exposures models, assuming that protective clothing and equipment were and were not used, are summarized in Table 3.6-1. Indications of exposure as a function of the AOEL are also included in Table 3.6-1.

The results obtained using the two estimation models demonstrate that in the worst case approximately xx.x % of the AOEL is accounted for (UK model smallest pack size, with large use rate, 50 ha/day, and no protective clothing). In more realistic scenarios less than x % of the AOEL is accounted for.

Table 3.6-1 Estimations of operator exposure related to the AOEL

Model	Operator Exposure 70 kg individual mg/kg bw per day	% of AOEL used
German Model – no protective clothing worn	0.0064	x.xx %
German Model – protective clothing worn	0.0033	x.x %
UK Model – no protective clothing worn	0.577	xx.x %
UK Model – protective clothing worn	0.012	x.x %

The following points, specific to the product OEC 2222, have been taken into account for the purposes of the estimations made. 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 is 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 is usual for the purposes of using 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 a 1 % default value for penetration through gloves (based on OEC 2222 being a solid formulation).

A study to determine operator exposure under conditions of actual use was not been conducted since the estimates made using worse case assumptions indicate that there is an acceptable margin of safety.

Table 3.6-2 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	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
Applicators wearing long pants, long sleeved shirts and no gloves			

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

3.6.3 Bystanders

Due to the low vapour pressure and inhalation toxicity of chemx, risks for bystanders as a result of inhalation of OEC 2222 are 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, UK and North American models and therefore is likely to be less than x % of the AOEL.

The proposed conditions of usage for OEC 2222 in agricultural practice pose no risks for possible spectators.

3.6.4 Workers

Data are not available to make a quantitative estimate of worker re-entry exposure. However the proposed use pattern for OEC 2222 is such that re-entry exposure will be minimal. Application is recommended early post-emergence when the crop height should be about 15 to 25 cm high. Workers may re-enter treated fields to monitor crops but this task would involve little foliar contact and thus minimal exposure. In addition, it is good husbandry practice not to enter treated fields until the plants are dry, without wearing protective clothing similar to that to be used by spray operatives, a precaution which will provide sufficient protection.

In the light of these considerations, the measurement of the level of exposure of agricultural workers likely to arise, has been not been undertaken. It is not necessary to establish a specific re-entry interval for the protection of workers.

3.6.5 Consumers

An assessment of the dietary intake of consumers was carried out using the UK, German, WHO European and North American diets. As there is only one proposed use (*i.e.* wheat), that was the only use taken into account for the purposes of the calculations. The TMDI was found to be < 1 % of the ADI. Accordingly it is considered that there is no health implication for the consumer associated with the ingestion of food [wheat] that was treated in accordance with GAP with chemx.

Chapter 4 Residues

4.1 Definition of the residues relevant to MRLs

4.1.1 Definition of the residues in wheat relevant to MRLs

Wheat metabolism study

In a metabolism study in wheat (Point IIA 6.2.1), the test material was applied pre-emergence and post-emergence at an exaggerated rate of application (3.5 x label rate *i.e.* 70 g as/ha). Residues were highest in foliage and straw and were just quantifiable in grain. Chemx parent was found to be the major component of the residue in wheat foliage and in straw accounting for 61 % and 37 % respectively. In wheat grain the residue level was very low (< 0.01 mg/kg) and was mostly either entrained in or incorporated into starch. Six metabolites were identified in foliage and straw. No single metabolite present accounted for 10 % of the residue. Identified metabolites amounted to approximately 13 and 14 % of the residue present in foliage and straw, respectively.

Of the six metabolites identified in wheat foliage and straw, two (desmethyl chemx and metabolite 2) were identified in the animal metabolism studies (rat, goat and hen). The remaining four metabolites identified in wheat foliage and straw were not observed in the animal metabolism studies.

The metabolic pathway in animals differed from wheat in that in wheat cleavage of the xxx bridge appears to be of greater significance than in animals, whereas in animals demethylation and chem3 ring hydroxylation appear to be more important. Since residues in treated wheat used for human and animal consumption are present in very low quantities and since each of the wheat metabolites not identified in animals (metabolite 10, xxx (metabolite 5) and metabolite 3) occurred individually at levels < 10 % and < 0.05 mg/kg in foliage and straw following treatment at 3.5 x label rate (*i.e.* 70 g as/ha), they are not considered to be of toxicological significance

Environmental chemistry and fate

In the environmental fate and behaviour studies, it was found that hydrolysis, microbial degradation and photolysis were the major degradation routes. Little or no volatilization or mineralization to CO₂ occurred, either in soil or in aquatic environments. Accordingly, application of chemx would result in the fairly rapid degradation of chemx (DT₅₀ ~ 30 days) to xxxxxxx (metabolite 2), metabolite 3 and desmethyl chemx. Chemx and xxxxxxx (metabolite 2) are bio-available and are taken up from the soil by plants, where they undergo further metabolism. Metabolite 3 is not bio-available. It remains bound to soil organic matter undergoing slower degradation.

Confined crop rotation study

Lettuce, radish, rye and barley were grown in boxes filled with a sandy loam soil (Point IIA 6.6.2). After sowing and during crop development, the boxes were maintained in screen-houses equipped with ventilation fans and windows. Crops were sown 30, 120, and 361 days after treatment. Re-sowings were also carried out at 60 and 89 days after treatment in the case of barley. The data generated in the confined crop rotational study demonstrated that application of chem2 and chem3 ¹⁴C-labelled-chemx to sandy loam soil at twice the proposed rate of application (*i.e.* 40 g as/ha), resulted in the occurrence of a higher proportion of chem2 labelled residues than expected. Residues of chemx, its xxxxxxx (metabolite 2) and chemx sugar conjugate in rotation crops (lettuce, radish, barley and rye) were ≤ 0.087 mg/kg. The highest amounts were found in cereal straw and hay

60 days after treatment. Soil metabolism resulted in the occurrence of high concentrations of the chem3-labelled metabolite 3 in soil. However, this metabolite was not taken up by plants and therefore was not included in the definition of the residue of concern.

Storage stability

In freezer storage stability studies (Point IIA 6.1.1), samples of ground wheat grain and forage were spiked with chemx at a level of 0.2 mg/kg and stored at -12°C (10°F) for 531 to 533 days. Since the common moiety method of analysis was used, the studies reported did not demonstrate the freezer storage stability of parent chemx residues or the storage stability of its individual metabolites in wheat, grain and forage. However, all tissue samples were frozen and subsequently analysed within a period of 533 days (18 months) and the common moiety method determined the majority of the total terminal residues present. Under these conditions, residues decreased by 11% and 10% in grain and forage respectively. The data reported indicate that residues of chemx were stable at -12°C (10°F) in grain and forage.

Proposed residue definition (food of plant origin)

On the basis of those considerations it could be proposed that chemx residues in wheat be regulated as chemx parent compound. However, given the specificity of the method of analysis developed and submitted, the proposed residue definition is “**the sum of chemx and its ethylsulfone metabolites, expressed as chemx**”. This definition is proposed to reflect the extent of the residue determined by the method of analysis submitted. It is considered that the method overestimates the residue of parent chemx by between 10 and 20 %.

4.1.2 Definition of the residues in food of animal origin relevant to MRLs

Animal metabolism

In the rat metabolism studies (Points IIA 5.1.1 to 5.1.3) more than 90 % of the chemx administered was excreted within 3 days of dosing. Parent chemx accounted for more than 80 % of the excreted ¹⁴C. In the goat study (Point IIA 6.4.1), > 85 % of the chemx administered was excreted within 3 days of dosing. Parent chemx was the major terminal residue identified in kidney (73 – 98 %), liver (81 – 86 %), muscle (72 – 89 %) and milk (19 – 37 %) of the extractable residues. The low levels of identified residues in muscle may be attributed to the higher level (≤ 35 % of the total terminal residue) of non-extractable residues.

In a hen study > 84 % of the administered dose was accounted for in excreta. In the majority of the tissues and in eggs, parent was the most abundant residue present, accounting for from 8 – 33 % of extractable residues.

In a goat metabolism study, unchanged chemx was the major terminal residue identified in liver, kidney, muscle and milk, accounting for 13 to 89.4 % of the total radioactive residue (0.0019 – 0.15 ppm). Other metabolites identified in liver, kidney, muscle and milk were xxxxxxxx (metabolite 2) at 6 to 25 % of the total radioactive residue (0.002 – 0.032 ppm), metabolite 1 at 1.1 – 10.7 % of the total radioactive residue (0.00099 – 0.015 ppm) and metabolite 11 at 1.5 to 18.9 % of the total radioactive residue (0.002 – 0.0057 ppm). Overall accountability was good. More than 85 % of the administered dose was excreted within 3 days of dosing. In both treatment animals tissues retained less than 0.02 % of the administered dose (0.31 – 0.37 ppm). Total radioactive residues in individual tissues were as follows: kidney and liver; 0.14 - 0.18 ppm, muscle; 0.0079 - 0.021 ppm, fat; < 0.0022 - 0.0079 ppm, while the levels in milk ranged from 0.027 - 0.030 ppm. Parent chemx was the major terminal residue identified in kidney, liver, muscle and milk accounting for 73 – 98 %, 81 – 86 %, 72 – 89 % and 19 – 37 %, respectively, of the extractable residues. The low levels of identified residues in

muscle may be attributed to the higher level ($\geq 35\%$ of the total radioactive residue) of non-extractable residues. The residues in fat were not characterised based of their low content. Overall, content of unextractable residues was low. Where unextractable residues were further characterised they appeared to contain both the chem2 and the chem3 moieties, indicating that they were mainly present as parent or its chem2 containing metabolites. The low level of apparent bioaccumulation was consistent with the log P_{ow} value of < 1 for parent chemx (range of pH 5-9).

Storage stability

In the freezer storage stability study carried out as part of a livestock feeding study (Point IIA 6.4.1), samples of ground animal matrices (milk, muscle and liver) were spiked with chemx at a level of 0.1 mg/kg and stored at -12°C (10°F) for 169 days. Since the common moiety method of analysis was used, the studies reported did not demonstrate the freezer storage stability of parent chemx residues or the storage stability of its individual metabolites in milk, muscle and liver. However, all tissue samples were frozen and subsequently analysed within a period of 169 days (18 months) and the common moiety method determined the majority of the total terminal residues present. Under these conditions, residues decreased by 5 - 8% (difference between $t=0$ and value at individual time points) in milk, muscle and liver. The data reported indicate that residues of chemx were stable at -12°C (10°F) in milk, muscle and liver for up to 169 days.

Proposed residue definition (food of animal origin)

On the basis of the data presented relating to metabolism of chemx in animals, it is evident that parent chemx is the major component of the residue in meat, meat by-products, milk and eggs. Accordingly it is the moiety which should be used for the purposes of defining the residue of concern. However, given the specificity of the method of analysis developed and submitted, the proposed residue definition is **“the sum of chemx and its ethylsulfone metabolites, expressed as chemx”**.

4.2 Residues relevant to consumer safety

The results of supervised field trials in wheat conducted across Canada, Europe and the USA have shown that residues in grain and straw collected at harvest following use as proposed (application at growth stage 39 – PHI 60 to 75 days) were below 0.01 mg/kg in the case of grain and were below and 0.1 mg/kg in the case of straw.

The potential exposure of consumers to chemx residues through dietary intake is very low. At the proposed recommended application rate of 20 g as/ha, residues of chemx are not expected to occur in wheat grain at levels greater than the 0.01 mg/kg limit of quantification. On the basis of the data generated in a livestock feeding study (point IIA 6.4.1), it is not expected that, consumption of feed commodities treated with chemx in accordance with the proposed label recommendations, will result in detectable residues in milk or tissues of lactating dairy cattle (< 0.004 mg/kg). Residues greater than 0.01 mg/kg are not expected to occur in animal products such as milk, eggs and meat, which are intended for human consumption.

Using the UK, German, WHO European and North American diets and considering direct wheat consumption, theoretical maximum daily intakes are below 0.2 % of the Acceptable Daily Intake (0.xx mg/kg bw/day calculated on the basis of the xx mg/kg/day NOEL identified in the chronic exposure study in rats, using a 100 safety factor). Taking into account potential intake from consumption of food of animal origin, the theoretical maximum daily intake is still below 1 % of the ADI. Accordingly there is a large safety margin for consumers.

4.3 Residues relevant to worker safety

Data are not available to make a quantitative estimate of worker re-entry exposure. However the proposed use pattern for OEC 2222 is such that re-entry exposure will be minimal. Application is recommended early post-emergence when the crop height should be about 15 to 25 cm high. Workers may re-enter treated fields to monitor crops but this task would involve little foliar contact and thus minimal exposure. In addition, it is good husbandry practice not to enter treated fields until the plants are dry, without wearing protective clothing similar to that to be used by spray operatives, a precaution which will provide sufficient protection.

4.4 Proposed MRLs and compliance with existing MRLs

4.4.1 Compliance with existing MRLs

Since the active substance is new there are no existing MRLs. The question of compliance with existing MRLs therefore does not arise.

4.4.2 Proposed MRLs

On the basis of the results of the extensive range of supervised field trials carried out with respect to the single use proposed for chemx, it is clear that residues in wheat grain will not exceed 0.01 mg/kg. On the basis of the proposal that the limit of quantification for control purposes be established at 0.02 mg/kg, it is proposed that the MRL for wheat be established at 0.02 mg/kg.

Following use in accordance with the proposed label directions, chemx residue levels in meat, fat, milk and egg are expected to be less than 0.01 mg/kg.

In the light of these considerations, and the GAP proposed for chemx - use on wheat at 20 g as/ha no later than growth stage 39 (PHI ~ 60 – 75 days) - MRLs for chemx are proposed as follows -

Wheat grain	0.02* mg/kg
Food of animal origin (meat, milk, eggs)	0.01 mg/kg

* at or about the limit of quantification

4.5 Proposed import tolerances

Since only one use is proposed, and since MRLs are proposed for the commodities in which residues are likely to occur, import tolerances are not required.

4.6 Basis for differences, if any, in conclusions reached having regard to established or proposed CAC MRLs

Since there are no established or proposed CAC MRLs and since data have not yet been submitted to the JMPR for consideration by it, the matter of differences in conclusions reached, does not arise.

Chapter 5 Fate and behaviour in the environment

5.1 Definition of the residue relevant to the environment

In the aerobic soil metabolism and the rate of degradation laboratory studies, three metabolites were identified in soil which were present in amounts > 10 % of the applied chemx. These metabolites were recovered at various time points: xxxxxxxx (metabolite 2) accounted for 15 % of the applied dose 225 days after application; desmethyl chemx accounted for 29 % of the applied dose 100 days after application; metabolite 3 accounted for 11% of the applied dose 100 days after application.

These three metabolites were also detected in the water/sediment study.

In field dissipation studies, following application at the maximum recommended use rate of 20 g as/ha to bare soil, the maximum content of chemx residues recovered in the 0 - 20 cm soil profile was 0.0017 mg/kg after 3 months and < 0.001 mg/kg after one year. Following application post emergence at 20 g as/ha the maximum content of chemx residue detected after 3 months was < 0.001 mg/kg chemx. The residue levels of xxxxxxxx (metabolite 2) + desmethyl chemx observed in soil after 3 months were 0.0033 mg/kg in bare plots and 0.0014 mg/kg in cropped soil and the maximum levels during the study were 0.0034 mg/kg in bare soil and 0.0022 mg/kg in cropped soil in the 0 - 20 cm soil horizon.

Methods of analysis have been submitted for the determination of chemx residues, chemx + metabolite 2 residues and chemx + metabolite 1 and metabolite 2 residues. All three methods are variants of a HPLC methodology involving quantitative conversion of analyte to the ethylsulfone metabolite by means of acid hydrolysis. The limit of quantification for the three methods is 0.0005 mg/kg.

On the basis of the maximum quantities of the three metabolites detected in laboratory incubation studies, the maximum concentrations to be expected in field soil following treatment at the recommended rate of 20 g as/ha is 0.001 mg/kg in the case of xxxxxxxx (metabolite 2), 0.0019 mg/kg in the case of desmethylchemx and 0.007 mg/kg in the case of metabolite 3. At such levels, the occurrence of residues of these three metabolites in soil can be considered as not being environmentally significant. The only residue of environmental significance is parent chemx.

Similar conclusions can be drawn with respect to residues of chemx in water.

It is therefore proposed that the residue be defined as **chemx (parent compound), determined as the ethylsulfone metabolite (metabolite 7), expressed as chemx.**

5.2 Fate and behaviour in soil

The metabolism and dissipation of chemx were investigated in detail under both laboratory and field conditions. Studies were performed using chemx labelled in the C-3 position of the chem2 ring and in the C-5 position of the chem3 ring labelled chemx and using equal mixtures of both radiolabelled forms. It was demonstrated that chemical hydrolysis and microbial degradation are the principal mechanisms of degradation, but photolytic degradation of chemx may also contribute to the dissipation of chemx in outdoor environments, particularly in aquatic systems.

In a 225-day aerobic soil metabolism study using a German loamy sand soil, (Speyer 2.2 standard soil, pH 5.8), in a closed system in darkness at 22 °C and 40 % water holding capacity, chemx (0.08 mg as/kg soil) was shown to degrade at a moderate rate with DT₅₀ of 51 / 54 days and DT₉₀ of 175 / 181 days, based on pseudo first order reaction kinetics. The principle metabolite was desmethyl chemx (29 % of applied radioactivity). Other

Appendix 10 Format for the Compilation of Tier III Overall Summaries and Assessments

Chemco	September 1997	Chemx (proposed ISO name)	page of
--------	----------------	---------------------------	---------

significant metabolites formed by cleavage of the xxx bond of chemx to form xxxxxxx (metabolite 2) (9 % of applied radioactivity) and xxxx (metabolite 10) (5 % of applied radioactivity) where the chem2 labelled material was applied to soil and metabolite 3 (3.4 % of applied radioactivity) where the chem3 labelled material was applied to soil.

The production of CO₂ was not a significant route of degradation although up to 8 % of the applied radioactivity was trapped as CO₂ over 100 days incubation. At the end of the 225-day incubation, 41 % of the applied ¹⁴C was present in the form of bound residues.

Studies were not conducted to elucidate the route of degradation in soil under anaerobic conditions, as it is not likely that such conditions will arise in practice and the issue is addressed in part in the aquatic metabolism study.

The photolysis of chemx was assessed over 30 days exposure of treated soil samples to natural sunlight (Richmond California). The degradation profile of chemx was similar for both light exposed and dark control, indicating that degradation was not directly the result of photolytic processes however the rate of degradation was faster in light exposed samples. The main photoproducts detected were xxxxxxx (metabolite 2) (~ 23 % of applied radioactivity) and metabolite 3 (*circa* 25 % of applied radioactivity) both products of hydrolytic cleavage.

While soil photo-degradation may contribute to the dissipation of chemx it is not a significant route of degradation. The calculated DT₅₀ value was *circa* 49 days.

The rate of degradation of chemx was assessed in three UK soil types (pH range 5.3 - 7.9) following up to 100 days incubation using both standard and modified incubation conditions and in two US soils (pH range 6.8 - 7.6) following up to 12 months soil incubation.

The half-life (DT₅₀) of chemx under the standard conditions varied from 92 days in Wick sandy loam soil to 226 days in Evesham clay loam soil. Following incubation in Evesham clay loam soil at an elevated MHC of 70 %, the DT₅₀ was reduced to 192 days, while incubation in the same soil at standard moisture content and lower temperature (10°C) resulted in a much slower degradation (DT₅₀ > 365 days). The major metabolites found in soil were xxxxxxx (metabolite 2) and metabolite 3 formed by cleavage of the xxx bond with maximum concentrations determined at 12.8 % and 10.6 % of the applied radioactivity after 100 days incubation, respectively. Desmethyl chemx was also formed (maximum concentration of 5.2 % of the applied radioactivity after 100 days). The study indicated that degradation rate may be pH dependant, with faster degradation at low pH values.

Chemx was found to be moderately persistent in both US soil types with DT₅₀ values ranging 31 - 37 days and DT₉₀ values ranging 206 - 262 days, using normal solvent extraction procedures. Two major transformation products, xxxxxxx (metabolite 2) and metabolite 3 and two minor transformation products, desmethyl chemx and metabolite 6, were identified. The major route of degradation was through cleavage of the xxx bond leading to the formation of metabolite 3 and xxxxxxx (metabolite 2), with a minor route involving the oxidative demethylation of chemx to form desmethyl chemx which degraded further to metabolite 6.

Total soil residues of chemx were shown to decline over the incubation period of 364 days to a maximum level of 21 % of the applied amount for the two US soils concerned. Soil binding was shown to be a major dissipation route for chemx in soil.

Studies on degradation of soil metabolites of chemx were not conducted since the levels likely to be present following use of OEC 2222 as proposed, are not considered to be environmentally significant. Estimates of the maximum environmental metabolite concentration likely to arise in field soil, made on the basis of the

Chemco	September 1997	Chemx (proposed ISO name)	page of
--------	----------------	---------------------------	---------

maximum levels detected in laboratory studies, the recommended rate of application and standard soil density, were 0.0007 - 0.0019 mg/kg soil.

In field studies conducted at eleven European sites the DT₅₀ ranged 11 - 47 days (mean 24 days) and DT₉₀ 131-358 days (mean 261 days) using the best fit kinetic function (Table 5.2-1). Maximum residue levels of chemx recovered in the 0 - 10 cm soil profile ranged from 0.0117 mg/kg at 20 g as/ha to 0.0191 mg/kg at 30 g as/ha applied to bare soil. There was no apparent correlation between soil type and degradation rate with chemx residues generally remaining in the 0 - 10 cm soil horizon.

The residue levels of chemx parent compound at the eleven European sites ranged from < 0.0005 to 0.0016 mg/kg in the 0 - 20 cm soil horizon three months after treatment and from < 0.0005 to 0.0007 mg/kg one year after a bare soil application at the maximum recommended rate of application of 20 g as/ha. Following post-emergent application at 20 g as/ha to a wheat crop, in accordance with the proposed recommendations for use, residues of chemx parent compound in soil 90 days after treatment ranged from < 0.0005 to 0.0007 mg/kg and one year after application, were from < 0.0005 to 0.0006 mg/kg.

The observation made on the basis of the results obtained in aerobic soil degradation laboratory study (point IIA 7.2.1, Grenfel RG 1995a) that degradation may be pH dependant with slower degradation in high pH soils, was not confirmed. In the two UK soil types pH 7.5/7.6 the DT₅₀ values were 25/23 days respectively. The characteristics of the soils tested did not appear to influence dissipation rate.

The maximum levels of xxxxxxx (metabolite 2) and of desmethyl chemx (metabolite 1) observed in the 0 - 20 cm soil horizon during were low at 0.0034 mg/kg following bare soil application, and 0.0022 mg/kg following post-emergent application. In general a higher proportion of metabolite residue occurred in the 10 - 20 cm horizon as compared to parent compound residue. **It is not anticipated that degradation products formed have any environmental significance.**

The results of the field trials conducted showed that even when applied to bare ground at up to 30 g as/ha chemx did not significantly migrate down the soil profile. As anticipated, **dissipation half-life (DT₅₀) in field soils is much faster than in laboratory studies - an average of 24 days for the eleven European sites and an average DT₉₀ of 261 days.** At higher use rates the ultimate dissipation of final soil residues may be prolonged as evidenced by studies at three German sites.

In soil dissipation studies conducted at two Canadian sites (Alberta and Saskatchewan) the dissipation of chemx and its major soil metabolite xxxxxxx (metabolite 2) was assessed following bare soil treatment. The half-life calculated (Gustafson and Holden 1990) was 52 days (Alberta site) and 13 days (Saskatchewan site)

Table 5.2-1 Summary of results of field soil dissipation studies with chemx

Country/Year	Study	Soil Characteristics					DT ₅₀ (days)	DT ₉₀ (days)
		Soil Texture			% OM	pH		
		% sand	% silt	% clay				
Belgium 1995/96	Field	5.1	80	14.9	3.3	7.1	12	131
Germany 1995/96	Field	18.6	55.1	26.3	1.4	6.1	47	247
Germany 1995/96	Field	70.6	25.5	3.9	1.9	6.0	28	303
UK 1995/96	Field	29.3	55.6	15.1	1.5	7.5	25	278
UK 1995/96	Field	46.9	31.1	22.0	1.0	7.6	23	252
France 1995/96	Field	16.9	71.6	10.2	1.3	6.0	25	276
France 1995/96	Field	16.5	49.6	32.1	1.8	6.4	11	302
France 1995/96	Field	13.8	57.8	26.2	2.2	6.0	32	358
Germany 1994/96	Field	57.8	35.3	6.9	1.9	6.5	26	285
Germany 1994/96	Field	11.2	71.1	13.7	1.7	6.7	22	243
Germany 1994/96	Field	44.6	44.8	10.6	2.2	7.1	18	197
Canada 1996	Field	60.0	20.0	20.0	2.3	8.0	52	1190
Canada 1996	Field	36.0	38.0	26.0	2.0	6.7	13	370

(Table 5.2-1). In the main chemx residues were confined to 0 - 15 cm horizon but residues were detected in the 15 - 30 cm horizon at various sampling intervals. Residues of xxxxxx (metabolite 2) were not detected in the Alberta site and only small amounts in the other site.

Since the DT₉₀ value was 261 days (< 1 year) and since soil residues recovered after one year following application at the recommended rate were < 0.0005 mg/kg (limit of quantification), it was not considered necessary that data on potential soil accumulation of chemx be generated and presented.

A study was performed in 2 US soil types and 3 UK soil types (pH range of 5.3 - 7.9) to assess the adsorption behaviour of chemx in soil. In all soil types tested chemx was mobile. There was little correlation between adsorption constants and with soil organic matter, but some positive correlation with soil pH. Determined K_{oc} values ranged 5.3 to 89 (average 33) indicating high potential soil mobility for chemx based on the ASTM classification system. Once adsorbed by soil colloids chemx was not readily desorbed (K_{oc} = 400). During the equilibration phase some degradation of chemx occurred, due presumably to hydrolysis - appropriate adjustments were made in the calculations reported.

Adsorption/desorption studies on the two main soil metabolites of chemx, xxxxxx (metabolite 2) and desmethylchemx performed in 2 US soil types and 2 UK soil types over the pH range 5.5 - 8.1, using the batch equilibrium method, were reported. Xxxxxx (metabolite 2) was highly mobile in both UK soil types (K_{oc} range 60 - 106) and moderately mobile in the US soil types (K_{oc} range 220 - 260). Desmethylchemx exhibited greater potential mobility over the same soil types K_{oc} = 36 in UK soils and ~ 110 in US soils. Based on the desorption constants obtained, it would appear that desmethylchemx once adsorbed has greater soil binding capacity than xxxxxx (metabolite 2).

The adsorption/desorption potential of metabolite 3 was determined in 4 US soil types. Determined K_{oc} values for metabolite 3 ranged 260 - 8280. Both K_d and K_{oc} values appeared to increase with increasing organic carbon content. The results obtained suggest moderate mobility in two soil types, Spinks loamy sand and Sarpy silt loam, low mobility in Drummer silt loam and immobility in Sable silt/clay loam.

Column leaching studies were not carried out, since reliable adsorption coefficients had been obtained in five soil types for chemx and in four soil types for xxxxxx (metabolite 2), desmethylchemx and metabolite 3.

On the basis of these studies, chemx can be classified as having high potential soil mobility, xxxxxxx (metabolite 2) and desmethylchemx as having high to moderately high potential soil mobility and metabolite 3 as having low to moderate mobility.

In an aged soil column leaching study, the results obtained indicated that chemx exhibits mobility in Speyer 2.1 soil columns although up to 23 % of the applied radioactivity was retained in the surface layer. The study also confirmed that both desmethylchemx and xxxxxxx (metabolite 2) are somewhat mobile in this soil while metabolite 3 has limited mobility. These findings are generally in accordance with the results of the adsorption/desorption studies reported. Since there was very limited degradation of chemx in the test soil ($DT_{50} > 100$ days), the study cannot be regarded as a good indicator of metabolite mobility. The results obtained were possibly influenced by the low microbial biomass of the test soil.

Preliminary results of a three-year lysimeter study conducted using a soil type that is susceptible to leaching were reported. The study, which involved use of radiolabelled material, was undertaken to clarify and quantify more fully the extent of mobility of chemx and its soil degradates under practical use conditions.

A recovery of *circa* 8 % of the applied radioactivity was obtained in the leachate. On analysis the leachate was shown to contain significant amounts of chemx (parent compound) at peak times together with a known soil metabolite xxxxxx (metabolite 6) (M9) and an unknown component (M10) both of which were present in quantities exceeding 0.1 µg/l.

None of the main soil metabolites identified - xxxxxxx (metabolite 2), desmethyl chemx - were detected in this study. Taken together with the low level of leaching of parent compound, these results suggest that strong binding to soil occurs, which is contrary to predictions made on the basis of the adsorption / desorption and column leaching studies. The absence of metabolite 3 in soil leachates is consistent with predictions based on adsorption/desorption studies - average $K_{oc} = 2495$ (Somerville A 1996).

The preliminary results reported for the lysimeter study suggest a low mobility of both chemx and its common soil metabolites in this sandy soil. Most of the radioactivity recovered in the leachate consisted of polar metabolites most of which are unidentified, apart from xxxxxx (metabolite 6) an identification that has yet to be confirmed using spectroscopic and other means.

Final conclusions from this study must await the assessment of the final report of the study and in particular an examination of the leachate data for the third year and examination of the residue data for the soil segments.

The study involved treatment with 30 g as/ha on both lysimeters while the proposed maximum rate of application for chemx is 20 g as/ha which proportionally should result in concentrations in the leachate being reduced by a third under normal use conditions (Volkel W and A Burgener 1997). Accordingly, following application at the recommended field rate (20 g as/ha) and assuming the leachate would contain residues in the same proportion as recorded in this study the expected mean concentrations of the two components M9 and M10 in the leachate would be 0.07 and 0.08 µg/L after two years.

Field leaching studies were not conducted since the preliminary results from the lysimeter study demonstrate a low potential for contamination of ground water sources following use of chemx as recommended.

Estimates of predicted environmental concentrations likely to arise in soil were presented (PEC_s) for initial and short-term exposure and were calculated on the basis of assumptions of 100 % and 50 % deposition in the top 0 - 5 cm and 0 - 10 cm soil horizons and off target deposition at 5 m distance assuming maximum drift of 0.6 % of the applied dose. The short-term time weighted average concentrations reported were calculated on the basis of the assumption of 100 % soil deposition and a DT_{50} value of 47 days, the highest value obtained in the field dissipation studies reported

On the basis of the recommended GAP and worst case exposure of bare soil, PEC_S values are 0.0267 mg/kg (0 - 5 cm soil horizon) and 0.0133 mg/kg (0 - 10 cm soil horizon). **Under practical realistic conditions of use PEC_S values can be expected to be in the range of 0.0133 mg/kg (0 - 5 cm soil horizon) and 0.0067 mg/kg (0 - 10 cm soil horizon).**

In the field dissipation studies reported, chemx residues were in the main confined to the 0 - 10 cm soil layer with recoveries in the 10 - 20 cm soil layer generally at the limit of determination. Residues of chemx recovered in the 0 - 10 cm soil layer, following bare soil treatment, ranged from 0.0026 - 0.0101 mg/kg on day 7, from 0.0016 - 0.0072 mg/kg on day 30, and from < 0.0005 - 0.0028 mg/kg on day 90. In cropped soil chemx residues in the 0 - 10 cm soil layer, ranged from 0.0024 - 0.0055 mg/kg on day 7, from 0.0021 - 0.0030 mg/kg on day 30, and from 0.0007 - 0.0013 mg/kg on day 90) based.

5.3 Fate and behaviour in water

In aqueous hydrolysis studies conducted using sterile buffer solutions at 25°C the hydrolytic half life of chemx was found to be 7, 48, 168 and 156 days at pH 4, 5, 7 and 9 respectively. Hydrolysis of chemx was found to be most rapid at acidic pH values and under elevated water temperatures. Xxxxxxx (metabolite 2) and metabolite 3 were the only significant hydrolysis products formed.

In aquatic systems, photolysis was shown to be a major route of degradation of chemx with a DT₅₀ of *circa* 36 hours equivalent to 3 x 12 hour sunshine days. Six photolytic degradation products that were formed in amounts ≥ 10% of applied radioactivity were identified (three from each label) during irradiation, while a further seven unidentified photolytic degradation products comprising < 10 % of applied radioactivity at any time point (maximum 8.74 % at 144 hours) were detected, 3 following irradiation of chem2 ring labelled ¹⁴C-chemx and 4 following irradiation of chem3 ring labelled ¹⁴C-chemx.

In a study of the direct phototransformation of chemx, the quantum yield was determined to be $\phi = 1.81 \times 10^{-3}$, and the DT₅₀ was found to be 5.7 hours. The differences in the photolysis half-lives determined in the two studies is ascribed to the lower solution concentration and the shorter path length in the quantum yield apparatus. When the quantum yield determination was used to provide an estimate of the environmental life time of chemx in Rhine river water, half life estimates were 2.4 - 3.8 days for Summer conditions at a depth of 0 - 30 cm and 21.7 - 33.4 days for Winter conditions at a depth of 0 - 30 cm. Aqueous photolysis is likely to be a significant mechanism for dissipation of chemx in aquatic environments.

In two water / sediment systems (pond pH 7.48 and river pH 7.1) incubated for 100 days, degradation of chemx (mixture of chem2 ring labelled (¹⁴C in the C-3 position) and chem3 ring labelled (¹⁴C in the C-5 position) chemx) was rapid at ambient temperatures (20°C) with DT₅₀ values of 16.1 and 19.5 days. In the case of the pond system maintained at low temperature (5.7°C), degradation was much slower with a DT₅₀ value of 58.3 days. In sterile systems degradation of chemx was much slower.

In these systems the decline of chemx from the aqueous phase was accompanied by a corresponding increase in sediment residues which represented > 50 % of applied material after 100 days incubation. Further extraction of the bound sediment residues confirmed that most of the applied radioactivity was associated with the humin, fulvic acid and humic acid fractions. In the total water sediment systems the main metabolite detected was desmethylchemx *circa* 13 % of applied radioactivity, with smaller amounts of xxxxxxx (metabolite 2) *circa* 6 % of applied radioactivity and metabolite 3 *circa* 1.5 % of applied radioactivity, which is consistent with the occurrence of hydrolytic breakdown followed by microbial degradation.

Chemco	September 1997	Chemx (proposed ISO name)	page of
--------	----------------	---------------------------	---------

In the supernatant water of both test systems, desmethylchemx comprised *circa* 10 % of the applied radioactivity, xxxxxxx (metabolite 2) comprised *circa* 4 % of applied radioactivity and metabolite 3 comprised *circa* 1.3 % of applied radioactivity, at peak concentrations. In the sediment layer of both systems chemx comprised *circa* 15 % of applied radioactivity, desmethyl chemx comprised *circa* 3 % of applied radioactivity, xxxxxxx (metabolite 2) comprised *circa* 2 % of applied radioactivity and metabolite 3 comprised 0.5 % of applied radioactivity at peak concentrations.

In crop protection practice the only likely potential exposure of surface water likely to arise is through potential spray drift at time of application. The highest PEC_{SW} values estimated for both drift and overspray relate to initial water concentrations and range from 0.012 to 2.0 µg as/L. The corresponding time weighted average PEC_{SW} values range from 0.0102 to 0.049 µg as/L depending on exposure route and captive water depth. The estimates presented are based on static water bodies (in the absence of standard methods for calculating concentrations in slow moving water bodies) and accordingly they may be regarded as worst case estimates under recommended use practice.

In view of the low content of degradation products in the lysimeter leachate and in view of the content of the metabolites detected in the water / sediment study, it was considered that significant concentrations of degradation products and metabolites are not likely to arise and accordingly no further PEC_S for surface water were calculated. It was therefore concluded that additional field testing is not warranted.

At recommended use levels neither chemx nor its metabolites are likely to be present in water bodies at levels of environmental significance. **As might be expected on the basis of the low application rate recommended, concentrations of chemx likely to arise in surface water are very low with a maximum concentration estimated to be 0.27 µg/L (0-30 cm) under worst case spray drift at 1 meter, 0.07 µg/L at 3 meter and 0.04 µg/L at 5 meter.**

Assuming that ground water concentrations of chemx will not exceed the maximum acceptable concentration (0.1 µg/L) for drinking water, the application of OEC 2222 will have no significant impact on water treatment procedures.

The data generated and reported (preliminary results) on the basis of the lysimeter study, provides a representation of the worst case scenario with respect to the occurrence of chemx residues in ground water - extreme sandy soil treated with 150 % of the recommended rate, mean precipitation rates over two years and successive applications in one lysimeter. The preliminary results reported indicate that chemx should not reach ground water in concentrations approaching 0.1 µg/litre.

Mean concentrations of chemx in lysimeter leachate were < 0.01 µg/L after two years following a single application and were 0.03 µg/L after two years following successive applications. Since the recommended application is 20 g as/ha with a single application per year it is unlikely that significant concentrations of chemx will reach ground water.

On the basis of the lysimeter studies two metabolites out of a possible twelve detected components were quantified with mean concentrations over the two-year period of *circa* 0.1 µg/L. One of these reaction products was found to co-chromatograph with the known metabolite xxxxxx (metabolite 6), while the other reaction product while close to xxxxxx on the chromatographic scale was not positively identified. The metabolite xxxxxx (metabolite 6) had a mean concentration of 0.1 µg/L in the leachate after two years with a single application and 0.07 µg/L after two years with successive applications. The metabolite of unknown identity had a mean concentration of 0.03 µg/L after two years with a single application and 0.12 µg/L after two years with successive applications.

Chemco	September 1997	Chemx (proposed ISO name)	page of
--------	----------------	---------------------------	---------

Other polar metabolites detected had mean concentrations below 0.1 µg/L (< 0.01 - 0.06 µg/l), while one component was detected at concentrations exceeding 0.1 µg/L following successive application.

On the basis of the recommended application rate of 20 g as/ha and taking account of proportionality, the content of these main metabolites in ground water are likely to be substantially below 0.1 µg/L. Accordingly it is believed that no significant metabolites, degradation or reaction products of chemx will arise in ground water sources and no predictions of likely concentrations are therefore necessary.

On the basis of the preliminary results of the lysimeter study, it appears unlikely that either chemx or its metabolites will pose a significant threat to ground water sources. However final conclusions must await the final report of the study.

5.4 Fate and behaviour in air

The vapour pressure of chemx is 3.05×10^{-8} Pa at 20°C and the calculated Henry's Law Constant at 20°C is 8.15×10^{-7} Pa/m³/mol (pH 5) and 8.83×10^{-9} Pa/m³/mol (pH 7). Since chemx is essentially non-volatile studies on volatilization were not considered necessary.

Contamination of the atmosphere by chemx is likely to be extremely low in field use, given its very low vapour pressure and the low rate of application recommended for OEC 2222 (80 % as). Atmospheric contamination is not considered to be a significant route of exposure in practice nor is it likely to be a significant source of environmental contamination

Chapter 6 Effects on non-target species

6.1 Effects on terrestrial vertebrates

The toxicity of chemx to birds is low (Table 6.1-1). The proposed manner of use of chemx suggests that exposure is likely to be mainly from consumption of treated foliage and associated avian food sources, with the greatest risk arising from oral ingestion of treated foliage. **The toxicity/exposure ratios calculated in respect of acute, short-term and sub-chronic exposure of birds feeding on a range of possible food sources, assuming worst case exposure (feeding exclusively on contaminated material), demonstrates that there is no significant practical risk to avian species (Table 6.1-2).**

Table 6.1-1 Toxicity of chemx to birds

Species	Exposure	Vehicle	NOEL / NOEC mg as/kg bw	LLD / LLC mg as/kg bw	LD ₅₀ / LC ₅₀ mg as/kg bw
Bobwhite Quail	acute oral	corn oil	xxx	> xxxx	> xxxx
Mallard Duck	acute oral	corn oil	xxxx	> xxxx	> xxxx
Bobwhite Quail*	5 day	acetone/ corn oil	xxxx	> xxxx	> xxxx
Mallard Duck*	5 day	acetone/ corn oil	xxxx	> xxxx	> xxxx
Bobwhite Quail	21 weeks	acetone/ corn oil	xxxx	-	-
Mallard Duck	22 weeks	acetone/ corn oil	xxx	-	-

* Based on day zero measured values

Table 6.1-2 Estimated food residues, maximum daily intake, acute short-term and sub-chronic toxicity/exposure ratios for birds following maximum field use of chemx (0.02 kg as/ha)

Bird Type	Body wt (kg) ¹ Food Uptake	Food Consumed	² Estimated Theoretical Exposure (mg as/kg bw/day)	³ TER _A	⁴ TER _{ST}	⁵ TER _{LT}
Small Bird	0.01 30 %	short grass	0.67	xxxx	xxxx	xxx
		leaves	0.19	xxxxx	xxxx	xxxx
		seeds/grains	0.02	xxxxxx	xxxxx	xxxxx
		small insects	0.18	xxxxx	xxxx	xxxx
		large insects	0.02	xxxxx	xxxxx	xxxxx
Large Bird	0.1 10 %	short grass	0.23	xxxx	xxxx	xxx
		leaves	0.06	xxxxx	xxxx	xxx
		seeds/grains	0.01	xxxxxx	xxxxx	xxxx
		small insects	0.06	xxxxx	xxxx	xxx
		large insects	0.01	xxxxxx	xxxxx	xxxx

¹ Food uptake in % of body weight

² ETE = Estimated food residue X daily intake/body weight

³ TER_A = LD₅₀/ETE (mg as/kg bw/day)

⁴ TER_{ST} = LC₅₀/ETE (mg as/kg food) [Toxicity data similar for both indicator species]

⁵ TER_{LT} = NOEC/ETE (mg as/kg food)

The main route of exposure for terrestrial vertebrates (*e.g.* mammals) to chemx will be through consumption of vegetation containing residues. Toxicity to terrestrial vertebrate species can be estimated from the mammalian toxicity studies conducted with chemx. For the purposes of risk assessment, the rat was used as a surrogate species (acute oral toxicity > 5,000 mg/as bw). The exposure routes considered significant are ingestion of short grass, leaves, small insects, large insects and grains. The acute toxicity / exposure ratios calculated in respect of terrestrial vertebrate species other than birds, feeding on a range of possible food sources, assuming worst case exposure (feeding exclusively on contaminated material), demonstrates that there is no significant risk associated with acute exposure to chemx for such species (Table 6.1-3).

Table 6.1-3 Estimated food residues, maximum daily intake and toxicity/exposure ratios for mammals following maximum field use of chemx (0.02 kg as / ha)

Mammal Type	Body weight (kg) Food Intake ¹	Food Consumed	Estimated Food Residue ² (mg as/kg/food)	Estimated Theoretical Exposure ³ (mg as/kg bw/day)	TER _A ⁴
Small Mammal	0.01 30 %	Short grass	2.240	0.67	7463
		Leaves	0.626	0.19	26316
		Seeds/grains	0.054	0.02	250000
		Small insects	0.590	0.18	27778
		Large insects	0.060	0.02	250000
Large Mammal	0.1 10 %	Short grass	2.240	0.23	21739
		Leaves	0.626	0.06	83333
		Seeds/grains	0.054	0.01	500000
		Small insects	0.590	0.06	83333
		Large insects	0.060	0.01	500000

¹ Food uptake in % of body weight

² kg as/ha x Hoerger and Kenaga Factors (1972)

³ ETE = Estimated food residue x daily intake/body weight

⁴ TER_A = LD₅₀/ETE (mg as/kg bw/day)

On the basis of the limited mammalian toxicity of chemx, it was considered that there was little point in calculated short-term toxicity exposure ratios.

The main route of long-term exposure for terrestrial vertebrates other than birds (*e.g.* mammals) to chemx will be through consumption of vegetation containing residues. Toxicity to terrestrial vertebrate species can be estimated from the mammalian toxicity studies conducted with chemx. For the purposes of risk assessment, the rat (90-day NOEL xxx mg/kg bw/day) and mouse (90-day NOEL xxx mg/kg bw/day) can be used as surrogate species. The exposure routes considered significant are ingestion of short grass, leaves, small insects, large insects and grains. **The long-term toxicity/exposure ratios calculated in respect of terrestrial vertebrate species other than birds, feeding on a range of possible food sources, assuming worst case exposure (feeding exclusively on contaminated material), demonstrates that there is no significant risk associated with such exposure to chemx for such species (Table 6.1-4).**

Note: Where in relation to any active substance, the toxicity / exposure ratios (TERs) estimated are indicative of potential risks for birds and other non-target terrestrial vertebrate species, it is necessary that refined risk assessments be performed, if appropriate, with the benefit of data from higher tier studies.

Table 6.1-4 Estimated food residues, maximum daily intake and long-term toxicity/exposure ratios for mammals following maximum field use of chemx (0.02 kg as / ha)

Mammal Type	Body weight (kg) Food Intake ¹	Food Consumed	Estimated Food Residue ² (mg as/kg/food)	Estimated Theoretical Exposure ³ (mg as/kg bw/day)	TER _{LT} ⁴
Small Mammal	0.01 30%	Short grass	2.240	0.67	Xx
		Leaves	0.626	0.19	Xxx
		Seeds/grains	0.054	0.02	Xxxx
		Small insects	0.590	0.18	Xxx
		Large insects	0.060	0.02	Xxxx
Large Mammal	0.1 10%	Short grass	2.240	0.23	Xxx
		Leaves	0.626	0.06	Xxx
		Seeds/grains	0.054	0.01	Xxxx
		Small insects	0.590	0.06	Xxx
		Large insects	0.060	0.01	Xxxx

¹ Food uptake in % of body weight

² kg as/ha x Hoerger and Kenaga Factors (1972)

³ ETE = Estimated food residue x daily intake/body weight

⁴ TER_{LT} = NOEL/ETE (mg as/kg food)

6.2 Effects on aquatic species

A summary of the aquatic toxicity of chemx is provided in Table 6.2-1. Testing for effects on sediment dwelling organisms were not conducted because of the absence of effects in invertebrate species at exposure levels likely to occur as a result of spray drift or runoff - direct application to water bodies is not anticipated. A bio-concentration study was not performed since the n-octanol / water partition co-efficient $\log P_{ow} < 1$. The highest PEC_{SW} values estimated relate to initial water concentrations and range from 0.012 to 2.0 µg as/L. The corresponding time weighted average PEC_{SW} values range from 0.0102 to 0.049 µg as/L depending on exposure route and captive water depth.

The toxicity of chemx to both freshwater and estuarine fish species and invertebrate species was extremely low both under acute and chronic exposure regimes. The main non-target species at risk in the aquatic environment are algae and aquatic plants, a finding that is to be expected in the case of a herbicide. The most sensitive species tested was the aquatic plant *Lemna gibba* (14 day IC₅₀ of x.xxxx mg/L and a NOEC of x.xxx mg/L).

Toxicity exposure ratios for the most sensitive aquatic test species were calculated for both acute and sub-chronic exposure. The TER_A values for all fish, invertebrate and algal species were one or more orders of magnitude greater than 100 and the TER_{LT} for fish and invertebrate species were one or more orders of magnitude greater than 10 for all exposure estimates.

The only aquatic species at risk from accidental exposure is the higher plant *Lemna gibba* for which the TER_A value was x.x for spray drift at 1 meter (0 - 30 cm) and xx for spray drift at 5 meter (0 - 30 cm). This is the only aquatic species likely to be affected as a consequence of use as proposed. While time weighted average exposure estimates indicate a potential for effects to continue, the fact that chemx is

dissipated rapidly in water bodies (DT₅₀ in water circa 18 days) should serve to minimize any such effects.

Table 6.2-1 Acute and chronic toxicity of chemx to aquatic organisms

Test Species	Test Duration	Test Conc.	No Effect Conc. (mg/l)	50 % Effect Conc. (mg/l)	Effect Parameter	Reference
<i>Oncorhynchus mykiss</i>	4 day	Measured	xx	> xx		Fisk R 1994 (a)
<i>Lepomis macrochirus</i>	4 day	Measured	xx	> xx		Fisk R 1994 (b)
<i>Cyprinus carpio</i>	4 day	Measured	xx	> xx		Fisk R 1995 (a)
<i>Cyprinodon variegatus</i>	4 day	Measured	xxx	> xxx		Fisk R 1995 (b)
<i>Oncorhynchus mykiss</i>	87 day	Measured	xxx	-	Survival/growth	Fisk R 1996 (a)
<i>Daphnia magna</i>	2 day	Measured	xx	> xx		Fisk R 1994 (c)
<i>Daphnia magna</i>	21 day	Measured	xxx	> xxx	Immobilisation/ Reproduction	Fisk R 1996 (6)
<i>Selenastrum capricornutum</i>	3 day	Nominal	< x.xxx	x.xxx	Biomass*	Rose A 1995 (a)
	3 day	Nominal	x.xxx	x.xxx	Growth rate	
	5 day	Nominal	x.xxx	x.xxx	Biomass**	
	5 day	Nominal	x.xxx	x.xxx	Growth rate	
<i>Scenedesmus subspicatus</i>	3 day	Nominal/ Measured	x.xx	x.x	Biomass**	Rose A 1995 (b)
<i>Anabaena flos-aquae</i>	5 day	Nominal	x.xx	x.xx	Biomass**	Rose A 1996 (a)
<i>Navicula pelliculosa</i>	5 day	Measured	xx	> xx	Biomass**	Rose A 1996 (b)
<i>Skeletonema costatum</i>	5 day	Measured	xxx	> xxx	Biomass**	Rose A 1996 (c)
<i>Lemna gibba</i>	14 day	Measured	x.xxxx	> x.xxx	FronD Inhibition	Rose A 1996 (d)

* Biomass calculated as area under growth curve

** Biomass calculated from cell density

In view of the low levels that are likely to occur in sediment following use as proposed and in view of the absence of significant effects in tests with aquatic invertebrate species, it is concluded that no significant threat exists for sediment dwelling species under practical conditions for use of chemx.

Note: Where in relation to any active substance, the toxicity / exposure ratios (TERs) estimated are indicative of potential risks for aquatic species, it is necessary that refined risk assessments be performed, if appropriate, with the benefit of data from higher tier studies.

6.3 Effects on bees and other arthropod species

The 48 hour oral LD₅₀ was > 30 µg as/bee and the 48 hour contact LC₅₀ was > 25 µg as/bee. On the basis of a single application of 20 g as/ha the determined hazard quotients for honeybees were QH_O < x.xx and QH_C <

x.xx. These values indicate that under practical conditions of use, an unacceptable risk will not arise for honeybees following acute exposure.

The effects of OEC 2222 on arthropod species other than honey bees was investigated in laboratory studies using artificial substrates with four representative test species - the carabid beetle, *Bembidion tetracolum*, the lycosid spider, *Paradosa spp.*, the phytoseiid mite, *Typhlodromus pyri* and the parasitic wasp *Aphidius rhopalosiphi* (Table 6.3-1). **The results of the tests which were carried out using a dosing rate equivalent to 30 g as/ha, which is substantially higher than the maximum application rate recommended for this compound (20 g as/ha), indicated that an unacceptable risk will not arise for such species following use as proposed.**

Table 6.3-1 Effect of OEC 2222 on four species of non-target arthropods

Species	Exposure Period	Observation	Reference
<i>Bembidion tetracolum</i>	14 day	No effect on survival, behaviour or food consumption - Harmless	Mead-Briggs 1994
<i>Paradosa spp.</i>	10-14 day	No effect on survival, behaviour or food consumption - Harmless	Mead-Briggs 1994
<i>Typhlodromus pyri</i>	7-14 day	No effect on survival, behaviour or fecundity - Harmless	Mead-Briggs 1996
<i>Aphidius Rhopalosiphi</i>	24-48 hour	No effect on survival behaviour or fecundity - Harmless	Mead-Briggs 1996

Note: Where in relation to any active substance, the hazard quotients (Q_H) estimated for honey bees or the toxicity / exposure ratios (TERs) estimated for non-target arthropod species are indicative of potential risks for such species, it is necessary that refined risk assessments be performed, if appropriate, with the benefit of data from higher tier studies.

6.4 Effects on earthworms and other soil macro-organisms

The acute toxicity of chemx to earthworms (*Eisenia foetida*) was determined following 14 days exposure in an artificial substrate. No adverse effects on behaviour, appearance or body weights were observed. The 14-day LC_{50} and NOEC for *Eisenia foetida* was > xxx mg as/kg dry soil.

The NOEC value is equivalent to a field application rate of > 838 kg as/ha - assuming soil bulk density to be 1.5 g/cm³, 100% deposition on the soil surface and even incorporation to a depth of 5 cm. The predicted initial and short term environmental concentrations of chemx in soil were estimated assuming 100 % and 50 % deposition in the top 0 - 5 and 0 - 10 cm soil horizon, based on the proposed recommendations for use and worst case exposure of bare soil. The PEC_S values obtained ranged from x.xxxx mg/kg (0 - 5 cm) to x.xxxx mg/kg (0 - 10 cm). Calculations made on the basis of the recommended crop protection practice resulted in PEC_S values ranging from x.xxxx mg/kg (0 - 5 cm) to x.xxxx mg/kg (0 - 10 cm). The TER_A for worst case exposure was xx,xxx, a value which is indicative of no unacceptable risk arising for earthworms following use of chemx as proposed.

On the basis of the results of field dissipation testing it can be concluded that predicted long-term environmental concentration in soil range from 0.0024 to 0.00101 mg as/kg after 7 days to 0.0005 to 0.0028 mg/kg after 90 days. The NOEC for chemx is xxx and the worst case long-term PEC_S value is 0.0101 and the TER_{LT} (7 day) = xx,xxx, the TER_{LT} (30 day) = xxx,xxx and the TER_{LT} (90 day) = xxx,xxx. **Accordingly it can be concluded that the risks arising for earthworms and other soil macro-organisms following use of chemx as recommended are insignificant.**

Note: Where in relation to any active substance, the toxicity / exposure ratios (TERs) estimated are indicative of potential risks for earthworms and other soil macro-organisms, it is necessary that refined risk assessments be performed, if appropriate, with the benefit of data from higher tier studies.

6.5 Effects on soil micro-organisms

The effects of OEC 2222 (80 % as) on soil microbial biomass and the nitrogen transformation of two agricultural soils were assessed over a 100 day exposure period. The test substance was applied at the recommended field rate and at a rate of application five times the recommended application rate.

OEC 2222 had no significant effect on soil biomass or mineral nitrogen level in sandy loam soil at either the recommended field rate or the five-fold field application rate. Similar results were obtained with the loamy sand soil treated at the recommended field rate of application. However, in loamy sand soil, at the five-fold field application rate, a significant effect on microbial biomass and nitrogen transformation was recorded on day 14 and 28. The treated soil had recovered by day 63.

Dinoseb acetate, a known respiratory inhibitor, which was used as a positive control treatment, caused a significant negative effect on biomass in the sandy loam soil but had little effect on the microbial population of the loamy sand soil, suggesting the presence of different microbial population. Nitrogen transformation was significantly different in both dinoseb acetate treated soils after 28, 63 and 100 days.

Table 6.5-1 Summary of effects of OEC 2222 on soil microbial activity

Soil Type	Treatment (mg OEC 2222/ kg soil)	Equivalent Field Rate (kg/ha)	Recommended Field Rate (kg/ha)	Effects on	
				Soil Biomass	Mineral Nitrogen
Sandy loam	0.038	0.023	0.02	No significant effect	No significant effect
	0.190	0.115	0.02	No significant effect	No significant effect
Loamy sand	0.038	0.023	0.02	No significant effect	No significant effect
	0.190	0.115	0.02	Transient effect on day 14 and 28 with recovery by day 63	

OEC 2222 when applied to two UK soil types at application rates equivalent to the recommended field rate and at a rate more than five times that rate, elicited only transient effects on soil micro-flora activity at the five-fold field rate. **It can thus be concluded that OEC 2222 applied at the normal recommended rate of application will not involve any significant risk for soil microbial communities under the proposed conditions for use of the product.**

Note: Where in relation to any active substance, the toxicity / exposure ratios (TERs) estimated are indicative of unacceptable effects on soil microbial activity, it is necessary that refined risk assessments be performed, if appropriate, with the benefit of data from higher tier studies.

6.6 **Effects on other non-target organisms (flora and fauna)**

The effects of chemx on the germination, seedling emergence, vegetative vigour and phytotoxicity of ten non-target plant species were assessed in laboratory screening studies. The results obtained suggested that pre-emergence application of chemx at the maximum proposed rate of application (20 g as/ha) did not effect the seed germination, emergence or survival of the non-target plant species tested. However plant height and dry weight of most species tested were reduced and phytotoxicity was observed. These effects were not observed following soil application of *circa* 1 g as/ha (5 % of the recommended application rate) which is equivalent to exposure by means of spray drift at a distance of one meter from the treatment area.

Following post-emergence application at the proposed field rate, radish was the only species for which survival was significantly reduced. Since chemx is a herbicide, phytotoxic effects on plant species contaminated by spray deposits are to be expected. However, using a one-meter spray buffer zone, exposure would be 5 % or less of the proposed application rate and should result in only slight injury to non-target plant species.

The degradation of chemx residues in soil and the resulting low level of field residues that can be recovered following treatment as recommended are such that no significant effects should occur on most plant species in subsequent crop rotations. **On the basis of its modest toxicity and of the anticipated low levels of residues likely to arise, it can be concluded that chemx should not have significant adverse effects on non-target flora and fauna.**

6.7 **Effects on biological methods of sewage treatment**

It is not considered likely that use of chemx as proposed will result in significant contamination of sewage treatment plants, consequently, risks to sewage treatment processes arising are considered to be low.

6.8 **Environmental risk mitigation**

On the basis of an assessment of risks for the environment associated with the proposed use of OEC 2222, two concerns have been identified -

- OEC 2222 is toxic to non-target terrestrial plants. If exposure of non-target terrestrial plants is greater than xx % of the proposed rate of application to the target crop, it is likely that there would adverse effects on the terrestrial wildlife habitat.
- OEC 2222 is toxic to aquatic plants. If exposure of aquatic plants is greater than x % of the proposed rate of application to the target crop, it is likely that there would be adverse effects on the aquatic wildlife habitat.

In order to protect sensitive non-target terrestrial and aquatic plants, buffer zones between last spray swath and the edge of the sensitive areas are proposed. The buffer zones proposed were calculated using the Nordby and Skuterud (1975) and Ganzelmeier (1995) models.

To protect terrestrial non-target plant species, a buffer zone of xx m is proposed between the last spray swath and the edge of sensitive terrestrial areas such as hedgerows, shelterbelts and woodland. To protect non-target aquatic plant species, a buffer zone of xx m is proposed between the last spray swath and the edge of sensitive aquatic areas such as wetlands, ponds, streams and open drains.

In addition, in order to protect non-target aquatic plant species from runoff, the following label statement is proposed - *Do not spray if heavy rain is forecast during or soon after application*

Chapter 7 Efficacy data and information

The example of an efficacy chapter of the summary and overall assessment that follows is intended to illustrate the approach recommended for the preparation of the chapter concerning efficacy data and information included in *Tier III* overall summaries and assessments, where such data and information is required by the Regulatory Authorities to which application is made.

Efficacy data and information is not required for all types of data submissions (*e.g.* those supporting the establishment of MRLs or import tolerances) or for the authorization or registration of plant protection products in some countries.

7.1 Effectiveness

7.1.1 Intended use

OEC 2222 is a foliar and residual acting herbicide for use as a spring post-emergence treatment in all cultivars of winter wheat. OEC 2222 suppresses the growth of couch grass and controls sterile and meadow brome as well as a wide range of weeds including mayweeds, cleavers and chickweed. The product is formulated as a water dispersible granule containing 80 % w/w of the active substance chemx.

Chemx is a new active substance belonging to the sulfonylurea class of herbicides. Sulfonylurea herbicides have a high rate of phytotoxicity to target plants allowing low volume usage. They also have low mammalian toxicity reducing any potential environmental hazard.

The following are the details of the preparation and of its proposed uses -

as:	chemx (80 % w/w)
Family:	sulfonylurea
Formulation:	water dispersible granule (WG)
Type:	post-emergence (spring) foliar & residual herbicide
Target organism:	certain grasses (couch grass, sterile brome and meadow brome) and some broad-leaved weeds (cleavers, mayweeds and common chickweed)
Crops:	winter wheat (excluding durum wheat).
Rate of Use:	25 g / ha
Latest application time:	Zadoks GS 39
Maximum number of treatments:	one

7.1.2 Mode of action

Sulfonylurea herbicides are readily absorbed by both leaves and roots and translocated in both the symplast and apoplast. The herbicide is tightly, though reversibly bound to the enzyme, acetolactate synthase (ALS), thus inhibiting ALS activity, which in turn prevents the synthesis of branched chain amino acids *e.g.* valine and

leucine. Chemx is therefore a potent inhibitor of cell division. In susceptible species the leaves become chlorotic and this is followed by death of the growing points. However, in some susceptible species, the leaves may remain green but they are stunted and non-competitive.

The rate of metabolism of chemx is the principal mechanism for differential tolerance or selectivity of plant species to sulfonylurea herbicides. Tolerant plant species render the herbicide non-phytotoxic - as in winter wheat - by means of rapid degradation, while it is slowly metabolised in susceptible species.

Sulfonylurea herbicides are considered to be moderately mobile in soil. Mobility generally increases with increasing soil pH and decreasing soil organic matter. Chemical hydrolysis and microbial breakdown are the most important methods of sulfonylurea degradation / dissipation in the soil. The rate of degradation of sulfonylurea herbicides in soil is greatest in warm, moist, light textured, low pH soils. Generally, the half-life of sulfonylurea herbicides in soils ranges from 1 to 8 weeks.

7.1.3 Crops

Winter wheat is the only crop on which data is presented and for which a label claim is made. OEC 2222 is **not** recommended for use on durum wheat.

7.1.4 Effectiveness against scutch (common couch) grass (*Agropyron repens*)

Proposed label claim: OEC 2222 is a foliar and residual herbicide for the suppression or scutch (couch) grass in winter wheat

For suppression of scutch (couch), apply with a surfactant, post-emergence after 1 February, between crop GS 13 to GS 39, provided the recommended weed stage (up to GS early tillering), has not been exceeded

Common scutch (couch) grass is the most important perennial grass weed in Europe. Currently there are no approved products for the suppression or control of scutch during the critical development period of winter wheat crops (from GS 30 - GS 79). The data reported was generated in a series of 32 trials conducted in the UK and Ireland in 1994 to 1997. Application rates of 10, 15, 20 and 40 g as / ha were evaluated. The minimum rate required to give consistent results was found to be 20 g / as / ha which corresponds to 25 g product / ha.

In some 10 trials, application was made to scutch grass at growth stages between 12 and 19. The level of control improved from an average of 30 % at a rate of 12.5 g product / ha to an average of 55 % for 25 g / product / ha when assessed between 31 to 41 days after treatment.

The activity of OEC 2222 was significantly improved with the addition of a surfactant that increased herbicide retention on leaves. Levels of control 100 to 114 days after treatment were shown to be 61 % for OEC 2222 at an application rate of 12.5 g product / ha, 76 % for OEC 2222 at an application rate of 25 g product / ha and 80 % for OEC 2222 at an application rate of 25g product / ha + OEC 088 at an application rate of 0.2 % v/v product / ha. No significant difference was apparent in the level of control achieved with either of the surfactants used - *Frigate* at 0.2 % v/v product / ha and OEC 088 at 0.2 % v/v product / ha. The level of control some 125 days after treatment was reduced (54 %) as a result of re-growth of rhizomes in these early growth stage treatments.

Chemco	September 1997	Chemx (proposed ISO name)	page of
--------	----------------	---------------------------	---------

In 13 trials treatments were applied where scutch was between GS 20 and GS 29 over a range of infestation levels. A single application of OEC 2222 (12.5 g product / ha), OEC 2222 (25 g product / ha) or OEC 2222 (25 g product / ha) + OEC 088 (0.2 % v/v product / ha) resulted in control of couch corresponding to values of 51 %, 59 % and 73 % respectively up to 104 days after treatment. Some evidence of suppression was still evident one year after a GS 29 treatment.

In 11 trials, single applications of OEC 2222 (12.5 product / ha), OEC 2222 (25 g product / ha) and OEC 2222 + OEC 088 (25 g product / ha + 0.2 % v/v product / ha) made between GS 30 and GS 32 resulted in average control levels of 57 %, 65 % and 84 % respectively 71 to 87 days after treatment.

Applications of 12.5 g product / ha, occasionally resulted in similar levels of effectiveness to those achieved using 25 g product / ha. However, greater consistency was achieved using 25 g product / ha and it is therefore proposed that the appropriate rate of use of OEC 2222 is 25 g product / ha with the addition of 0.2 % v/v of a recommended surfactant.

The mean level of scutch (couch) control achieved using OEC 2222 + OEC 088 (25 g + 0.2 % v/v product / ha) is considered to be commercially acceptable. The suppression of scutch during crop development can help to maintain both quality and yield, by reducing competition for nutrients and decreasing the risk of lodging and other problems associated with high levels of green matter at harvest.

The proposed label claim of suppression of scutch (couch) grass using OEC 2222 at 25 g product / ha, with the addition of a surfactant, is justified.

7.1.5 Effectiveness against sterile brome (*Bromus sterilis*)

Proposed label claim: OEC 2222 is a foliar and residual herbicide for the control of sterile brome in winter wheat

For control of sterile brome (moderately susceptible), apply with a surfactant, post-emergence after 1 February, between crop GS 13 to GS 39, provided the recommended weed stage (up to GS early tillering), has not been exceeded

Sterile brome is the most common brome species in European wheat and is increasingly becoming a problem where reduced tillage operations are practised. There is currently no herbicide commercially available which provides a high level of control of this weed species.

Some 19 trials were conducted in the UK in which OEC 2222 was applied to sterile brome, between 1994 and 1997. Levels of control achieved were high, especially when the product was applied between weed growth stages 13 and 29. Control levels generally ranged between 84 % and 94 % - there were a few instances of up to 100 % control. The minimum rate of application necessary to achieve a consistent level of control was 25 g product / ha with a surfactant at 0.2 % v/v product / ha. No significant difference was apparent in the level of control achieved using OEC 2222 with either of the surfactants used - *Frigate* at 0.2 % v/v product / ha and OEC 088 at 0.2 % v/v product / ha.

The proposed label claim that sterile brome up to early tillering is moderately susceptible to OEC 2222 at 25 g product / ha, with the addition of a surfactant, is justified.

7.1.6 Effectiveness against meadow brome (*Bromus commutatus*)

<p>Proposed label claim: OEC 2222 is a foliar and residual herbicide for the control of meadow brome in winter wheat</p> <p>For control of meadow brome, apply with a surfactant, post-emergence after 1 February, between crop GS 13 to GS 39, provided the recommended weed stage (up to GS mid-tillering), has not been exceeded</p>
--

Three trials were carried out on meadow brome in the UK. Levels of control achieved were excellent at a rate of application of 25 g product / ha, with a surfactant 0.2 % v/v product / ha.

The proposed label claim that meadow brome up to mid-tillering is susceptible to OEC 2222 at 25 g product / ha, with the addition of a surfactant, is justified.

7.1.7 Effectiveness against cleavers (*Gallium aparine*)

<p>Proposed label claim: OEC 2222 is a foliar and residual herbicide for the control of cleavers in winter wheat</p> <p>For control of cleavers (moderately susceptible), apply with a surfactant, post-emergence after 1 February, between crop GS 13 to GS 39, provided the recommended weed stage (GS up to 15 cm tall), has not been exceeded</p>
--

The results of 17 trials conducted in the UK in the period 1994 to 1996 were reported. The results obtained demonstrate that cleavers are moderately susceptible to OEC 2222 when the product is applied between weed GS 12 to 23. Control is significantly improved when a surfactant is added. While adequate levels of control were achieved in some trials using an application rate of 12.5g product / ha, greater consistency was achieved when a rate of 25g product / ha was used.

The proposed label claim that cleavers up to 15 cm tall is moderately susceptible to OEC 2222 at 25 g product / ha, with the addition of a surfactant, is justified.

7.1.8 Effectiveness against mayweeds (*Matricaria spp.*)

<p>Proposed label claim: OEC 2222 is a foliar and residual herbicide for the control of mayweeds in winter wheat</p> <p>For control of mayweeds (moderately susceptible), apply with a surfactant, post-emergence after 1 February, between crop GS 13 to GS 39, provided the recommended weed stage (GS up to 4 leaves), has not been exceeded</p>
--

The results of some 25 trials with OEC 2222 for the control of mayweed conducted in the UK and Belgium during the period 1994 to 1996 were reported. The results obtained demonstrated that OEC 2222 has good activity against mayweeds, although the level of control achieved was not as consistently high as that obtained using the standard treatment *Harmony M*®. The levels of control achieved following application at 12 g, 18.75 g, 25 g and 50 g were 43 %, 45 %, 54 % and 67 %, respectively, some 32 - 34 days after treatment. The levels of control improved to 67 %, 66 %, 82 % and 85 % by 71 to 78 days after treatment. There was however a

wide range of variation around these mean figures. The minimum rate of application necessary to give consistent results was 25g product / ha. The level of control achieved was significantly improved by the addition of a surfactant.

The proposed label claim that mayweeds up to the 4 leaf stage are moderately susceptible to OEC 2222 at 25 g product /ha, with the addition of a surfactant, is justified.

7.1.9 Effectiveness against common chickweed (*Stellaria media*)

Proposed label claim: OEC 2222 is a foliar and residual herbicide for the control of common chickweed in winter wheat

For control of common chickweed (moderately susceptible), apply with a surfactant, post-emergence after 1 February, between crop GS 13 to GS 39, provided the recommended weed stage (GS up to 6 leaves), has not been exceeded

The results of 13 trials with OEC 2222 for the control of common chickweed conducted in the UK in the period 1994 - 1996 were reported. The level of control was shown to improve and be more consistent following application of 25 g product / ha as compared to application of 12.5 g product /ha. The 25 g product / ha rate of application is therefore recommended. Levels of control achieved ranged from 68 % to 100 % depending on rate of application and timing of treatment. The addition of a surfactant to the spray mixture (*Frigate* or OEC 088 at 0.2 % v/v) greatly improved the activity of OEC 2222 against chickweed - levels of control achieved with the mixture were close to 100 %.

The proposed label claim that common chickweed up to the 6 leaf stage is moderately susceptible to OEC 2222 at 25 g product /ha, with the addition of a surfactant, is justified.

7.2 Information on the occurrence or possible occurrence of the development of resistance

Resistance is unlikely to develop. Should resistant populations arise, their control can be achieved through the use of alternative products. While there is some evidence of population resistance developing to sulfonylureas in situations of repeated use (especially in relation to chickweed), this is unlikely to occur in the context of the proposed use of OEC 2222.

The possibility of the development of resistance in scutch (couch) grass is being investigated. When available the report generated will be provided.

7.3 Effects on the yield of treated plants or plant products in terms of quantity and/or quality

7.3.1 Effects on the quality of plants or plant products

There is no evidence that OEC 2222 has any effects on the quality of plants or plant products.

7.3.2 Effects on transformation processes

There is no evidence that OEC 2222 has any effects on transformation processes.

7.3.3 Effects on yield of treated plants or plant products

A total of 16 trials were taken to yield and assessed for any effects of application of OEC 2222, in the absence of weeds. Generally there were no significant negative effects on the yield of winter wheat when the product was applied at the recommended rate of 25 g / ha with or without the surfactant OEC 088. In addition, no significant reductions in yield occurred at the 2n rate compared to the untreated controls. The reduction in yield observed in two trials was considered to be due to poor crop establishment and the effects of stress resulting from drought following treatment.

A total of 20 trials were taken to yield and assessed for any yield effects in the presence of weeds. Significant yield increases were observed in most trials with increases ranging from 6 % to 69 % depending on the time and rate of application. The later the application timing the less marked was the increase in yield. The increase in yield was more pronounced when a surfactant was used.

7.4 Phytotoxicity to target plants (including different cultivars), or to target plant products

Assessments for the phytotoxic effects of OEC 2222 were made in a total of 73 trials. There were no necrotic effects or crop vigour effects in any of the trials at any time of assessment. The occurrence of chlorosis was noted in four trials, following applications made at growth stages ranging from GS 21 - GS 39. In all cases, the chlorotic effects observed were mild and were transient.

Two trials were carried out to assess the potential phytotoxicity of OEC to winter wheat varieties. Some 42 varieties were assessed in one trial while 49 varieties were assessed in the second trial. There were no phytotoxic effects observed in any variety at any assessment timing.

There were no phytotoxic effects observed as a result of the addition of either adjuvant to the OEC 2222 spray mixture - OEC 088 or *Frigate*.

7.5 Observations on undesirable or unintended side effects e.g. on beneficial and other non-target organisms, on succeeding crops, other plants or parts of treated plants used for propagating purposes (e.g. seed, cuttings, runners)

7.5.1 Impact on succeeding crops

A total of 105 trials were assessed for phytotoxic effects arising in following crops, (linseed, spring peas, winter peas, spring barley, winter barley, winter wheat, winter beans, sugar beet and winter oilseed rape), following application of OEC 2222.

No phytotoxic effects were observed in any trial in which winter wheat or winter beans were grown as following crops. In the case of peas, sugar beet, winter barley and winter oilseed rape, mild chlorosis, reduced stand and reduced biomass were observed in some trials. The effects were generally less severe than those observed following the use of the standard treatments (metsulfuron-methyl 7 % w/w + thifensulfuron-methyl 68 % w/w) and (triasulfuron 20 % w/w).

In the event of crop failure, winter wheat is the only crop that should be sown in the same cropping year.

7.5.2 **Impact on adjacent crops**

In a trial conducted with field peas (*Pisum sativum var. arvense*) in which OEC 2222 was applied in conditions in which wind speed was slightly higher than the recommended maximum wind speed for a conventional hydraulic ground sprayer, it was demonstrated that spray drift did not exceed levels occurring with conventional herbicides. The distance at which no symptoms of damage were found was 4.5 m.

7.5.3 **Impact on seed viability**

Chemx treated winter wheat grains were tested to determine their germination rates and early growth in the field. It was concluded that there was no effect on the germination capacity and early growth of plants grown from seed exposed to a treatment of OEC 2222.

7.5.4 **Impact on beneficial and other non-target organisms**

No effects on beneficial or other non-target species were observed in any of the field trials carried out to assess either the effectiveness or phytotoxicity of OEC 2222.

7.6 **Conclusions**

OEC 2222 is a useful new plant protection product of particular value for the suppression of scutch (couch) grass and the control of sterile brome as an “in crop” treatment, thereby filling a niche in the weed control market. Its novel chemistry which allows application to winter wheat is timely, given the increasing trend towards cultural practices such as non-inversion tillage, minimal cultivation and continuous wheat cropping, which limit opportunities to control grass weeds with conventional herbicides.

OEC 2222 also gives useful control of some broadleaf weeds, especially cleavers that are frequently problematic in headlands - an area where scutch and sterile brome are most prevalent.

OEC 2222 is safe to use, being non-phytotoxic and relatively benign to non-target organisms. Being a sulfonyleurea compound, care must be taken when applying the product in situations which are adjacent to broadleaf crops. Thorough cleaning of application equipment after spray application is essential.

Table 7.6-1 Summary

Crop:	Winter Wheat	
Varieties:	All	
Application Timing:	Apply post-emergence of the crop only in the spring (after February 1st), from the three expanded true leaf stage (GS 13) onwards up to flag leaf ligule just visible (GS 39), provided the recommended weed stages have not been exceeded	
Product:	OEC 2222	
Dose Rate:	25 grams / hectare	
PLUS		
Additional recommended surfactant:	0.2 % v/v spray volume	
Weed Species Controlled:		
Broadleaved Weeds	Susceptibility	Growth stage controlled
Common Chickweed	MS	Up to 6 leaves
Mayweeds	MS	Up to 4 leaves
Cleavers	MS	Up to 15 cm tall
Grass Weeds	Susceptibility	Growth stage controlled
Meadow brome	S	Up to mid-tillering
Sterile brome	MS	Up to early tillering
Scutch (Couch)	Suppression	Up to early tillering
Susceptibility Ratings:	S = Susceptible; MS = Moderately Susceptible; Suppression = Reduction in plant biomass but incomplete control	

Chapter 8 Overall Conclusions

Chemx is the proposed ISO common name for xxxxxxxxxxxxxxxxxxxxxxxxx. Chemx is a selective, contact and residual sulfonylurea herbicide for use on winter wheat at a maximum application rate of 20 g as/ha. It has activity against scutch (couch) grass, sterile and meadow brome as well as a wide range of broad leafed weeds including mayweeds, cleavers and chickweed.

Chemx has a low order of acute toxicity by the oral, dermal and inhalation routes. It is not classified with respect to dermal or ocular irritancy (does not satisfy the classification criteria) and does not cause dermal sensitisation in the system tested. In the series of sub-chronic and chronic toxicity tests conducted in the rat, mouse and dog, the target organ was identified as being the kidney and urinary bladder in all three species. Adverse effects were demonstrated at high dose levels and were considered to be the result of mechanical injury caused by substance crystallisation in the urine.

An ADI of x.xx mg/kg bw/day was proposed using a safety factor of 100 and the lowest NOEL of xx mg/kg bw/day observed in the chronic toxicity rat feeding study. An AOEL was proposed using the NOEL from the sub-chronic and one-year dog studies of xxx mg/kg bw/day and a 100-fold safety factor. It was demonstrated that there is an adequate margin of safety for operators from the single use scenario proposed. A drinking water limit of - maximum allowable concentration (MAC) - xxxx µg/L is proposed.

The level of residues detected in treated grain was below the limit of quantification. The following MRLs are proposed:-

wheat grain	0.02 * mg/kg
Food of animal origin (meat, milk, eggs)	0.01 mg/kg

* at or about the limit of quantification

On the basis of the environmental fate data generated, it was demonstrated that, at the levels of use proposed, significant residues would not persist in soil. It is suggested that following application in accordance with good plant protection practice, chemx residues will not have unacceptable effects on the environment.

In due course, the final results relating to the extent and nature of metabolites detected in the long term field lysimeter study will be provided. On the basis of the interim results available it is considered unlikely that chemx or its metabolites will pose a significant threat to ground water sources following use as proposed.

The ecotoxicological data presented indicate a low risk potential for non-target terrestrial species, other than non-target plants, when used in accordance with good plant protection practice. The only other compartment for which a practical risk may arise is in respect of aquatic habitats where the higher plant *Lemna gibba* is potentially at risk from spray drift and runoff.

When used as proposed, no significant risk to non-target organisms, including soil organisms should arise.

Proposed decision

It is proposed that OEC 2222 of the specification submitted be authorized for use as a plant protection product for the control of certain weeds in winter wheat and that the authorization be conditional on the provision of additional data and information as specified hereunder.

Appendix 10 Format for the Compilation of *Tier III* Overall Summaries and Assessments

Chemco September 1997 Chemx (proposed ISO name) page of

Further information to be submitted

- IIIA 2.7.5 Shelf life test following storage for 2 years at ambient temperature
 - IIA 4.2.1 Validation of the method of analysis for the active substance as manufactured
 - IIA 4.4 Validation of the methods of analysis for residues in soil with respect to metabolite 1 and metabolite 2
 - IIA 4.5 Validation of the methods of analysis for residues in water soil with respect to metabolite 2
 - IIA 4.7 Validation of the methods of analysis for residues in air
 - IIA 7.4.7 Final Report of the long-term lysimeter study
-

List of end points for the active substance chemx

Chapter 1: Identity, physical and chemical properties, details of uses, further information, and proposed classification and labelling

Active substance (ISO Common Name)	Chemx
Function (e.g. fungicide)	Herbicide
Rapporteur Member State	Ireland

Identity (OECD data point number IIA 1)

Chemical name (IUPAC)	
Chemical name (CA)	
CIPAC No	None
CAS No	16335-17-2
EEC No (EINECS or ELINCS)	None
FAO Specification (including year of publication)	None
Minimum purity of the active substance as Manufactured (g/kg)	980
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	None identified.
Molecular formula	
Molecular mass	440.37
Structural formula	

Physical and chemical properties (OECD data point number IIA 2)

Melting point (state purity)	201.1 - 201.7 (99%)
Boiling point (state purity)	not relevant
Temperature of decomposition	No data
Appearance (state purity)	White powder, munsell colour N 9.5/90% R (98.9%)
Relative density (state purity)	1.5185 g/cm ³ (99.5%)
Surface tension	66.6 N/m
Vapour pressure (in Pa, state temperature)	3.05 x 10 ⁻⁸ at 20°C [by extrapolation]
Henry's law constant (Pa m ³ mol ⁻¹)	8.15 x 10 ⁻⁷ Pa/m ³ /mol [pH 5], 8.83 x 10 ⁻⁹ [pH 7] , 2.97 x 10 ⁻⁸ [pH 9]
Solubility in water (g/l or mg/l, state temperature)	pH 5: 17.6 ± 2.71 at 20°C.
	pH 7: 1626.8 ± 39.8 at 20°C.
	pH 9: 482.44 ± 8.35 at 20°C.
Solubility in organic solvents (in g/l or mg/l, state temperature)	Heptane < 0.001 g/L at 20°C.
	Xylene 0.16 g/L at 20°C.
	1,2 Dichloromethane 4.35 g/L at 20°C.
	Methanol. 0.33 g/L at 20°C.
	Acetone 0.71 g/L at 20°C.
Ethyl acetate 1.01 g/L at 20°C.	
Partition co-efficient (log P _{ow}) (state pH and temperature)	pH 5: log P _{ow} = < 1
	pH 7: log P _{ow} = < 1
	pH 9: log P _{ow} = < 1
Hydrolytic stability (DT ₅₀) (state pH and temperature)	pH 4: t _{1/2} = 7 days at 25°C.
	pH 5 : t _{1/2} = 48 days at 25°C.
	pH 7: t _{1/2} = 168 days at 25°C.
	pH 9: t _{1/2} = 156 days at 25°C.
Dissociation constant	pKa = 3.51 at 20° C in the range pH 1.1 - 6.98.
UV/VIS absorption (max.) (if absorption > 290 nm State ε at wavelength)	λ max = 208 nm. The molecule's absorption spectrum extends to 320nm. ε= 4169 at λ= 300nm and ε= 2188 at λ = 312nm.
Photostability (DT ₅₀) (aqueous, sunlight, state pH)	At pH 7 in aqueous sterile buffered water t _{1/2} was determined to range from 1.6 - 2.1 days natural sunlight
Quantum yield of direct phototransformation in Water at λ > 290 nm	Quantum yield calculated to be Φ = 1.81 x 10 ⁻³
Flammability	Chemx is not flammable.
Explosive properties	Chemx is not explosive.

Summary of intended uses

Crop and/or situation (a)	Country	Product name	F G or I (b)	Pests or Group of pests Controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	g/ as/hL min max	water L/ha min max	g as/ha min max		
Wheat [Winter]	USA Canada EU N & S regions	OEC 2222	F	<i>Agropyron repens;</i> <i>Bromus sp.</i> <i>Galium aparine;</i> <i>Stellaria media;</i> <i>Matricaria sp..</i>	WG	800		GS 13-39	1 1			8 - 10	200 - 250	20	* Wheat is tolerant to OEC 2222 at growth stage 13, but spraying is prohibited until the Spring, after the Winter stop in growth. Spraying in Autumn is prohibited, for environmental reasons, even if the crop has reached Growth Stage 13.

- (a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (e.g. fumigation of a structure)
- (b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
- (c) e.g. biting and suckling insects, soil born insects, foliar fungi, weeds
- (d) e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
- (e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
- (f) All abbreviations used must be explained
- (g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench

- (h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plant - type of equipment used must be indicated
- (i) g/kg or g/l
- (j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
- (k) Indicate the minimum and maximum number of application possible under practical conditions of use
- (l) PHI - minimum pre-harvest interval
- (m) Remarks may include: Extent of use/economic importance/restrictions

Classification and proposed labelling (OECD data point number IIA 10)

with regard to physical/chemical data	<p>Classification: None required.</p> <p>Proposed label:</p> <p>Symbol: None required</p> <p>Indication of danger: None required</p> <p>Risk phrases: None required</p> <p>Safety phrases: None required</p>
with regard to toxicological data	<p>Classification: None required</p> <p>Proposed label:</p> <p>Symbol: None required</p> <p>Indication of danger: None required</p> <p>Risk phrases: None required</p> <p>Safety phrases: Keep out of reach of children Refer to special instructions / safety data sheet</p>
with regard to fate and behaviour data	<p>Classification: None required.</p> <p>Proposed label:</p> <p>Symbol: None required</p> <p>Indication of danger: None required</p> <p>Risk phrases: None required</p> <p>Safety phrases: Avoid release to the environment</p>
with regard to ecotoxicological data	<p>Classification: None required.</p> <p>Proposed label:</p> <p>Symbol: None required.</p> <p>Indication of danger: None required.</p> <p>Risk phrases: None required.</p> <p>Safety phrases: Avoid release to the environment</p>

Chapter 2: Methods of analysis

Analytical methods for the active substance (OECD data point number IIA 4.2)

Technical as (principle of method)	Analysis by HPLC with UV detection following dissolution in acetone.
Impurities in technical as (principle of method)	Analysis by HPLC with UV detection following dissolution in dioxane.
Plant protection product (principle of method)	Analysis by HPLC with UV detection following dissolution in acetonitrile.

Analytical methods for residues (OECD data point number IIA 4.3)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Residue extracted in acetonitrile/water [90:10], hydrolysed to the "Sulphone" common analyte and analysed by HPLC with fluorescence detection. An appropriate LOQ is 0.02 or 0.05mg/kg.
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Residue extracted in acetonitrile/water [90:10], hydrolysed to the "Sulphone" common analyte and analysed by HPLC with fluorescence detection. LOQ is not required, as a residue definition is not required.
Soil (principle of method and LOQ)	Residue extracted in MeOH/ 1N HCl [70/30], hydrolysed to the common "Sulphone" analyte and analysed by HPLC with fluorescence detection. [Separation of parent from xxxxxxx and/or the desmethyl metabolites is achieved if required by either acidic alumina or florisil column clean-up] Methods validated to 0.5 µg/kg in soil.
Water (principle of method and LOQ)	Water samples are made acidic with acetic acid. The sample is passed through an SPE- RP cartridge and the elute is cleaned-up using an SPE-SAX followed by an SPE-alumina cartridge. The final extract is made up in acetonitrile/water (1:9) prior to being analysed using HPLC with UV detection. The method was validated for residues of chemx in the range 0.1-10.0 µg/L for both drinking and surface water. Independent validation was also provided.
Air (principle of method and LOQ)	A method of analysis was supplied which used tenax to adsorb residues from the air. The residues were desorbed using acetone and were analysed using HPLC with UV detection.
Body fluids and tissues principle of method and LOQ)	No data required

Chapter 3: Impact on human and animal health

Absorption, distribution, excretion and metabolism in mammals (OECD data point number IIA 5.1)

Rate and extent of absorption:	> 90% of low dose; 35 – 40 % of high dose
Distribution:	all tissues
Potential for accumulation:	Nil
Rate and extent of excretion:	Excretion was rapid; > 80% and > 90% within 24 and 48 h post-dose, respectively. The major route was urinary at the low dose (77 – 87 %) and <i>via</i> the faeces at the high dose (55 – 63 %).
Metabolism in animals	Up to 88% of dose excreted as parent. Demethylation and chem2 ring hydroxylation occurs to a limited extent (cleavage of the xxxx bond is very limited).
Toxicologically significant compounds (animals, plants and environment)	Mainly parent.

Acute toxicity (OECD data point number IIA 5.2)

Rat LD ₅₀ oral	> 5000 mg/kg
Rat LD ₅₀ dermal	> 5000 mg/kg
Rat LC ₅₀ inhalation	> 3.0 mg/L
Skin irritation	Non-irritant
Eye irritation	Moderately irritant
Skin sensitisation (test method used and result)	Non sensitising

Short term toxicity (OECD data point number IIA 5.3)

Target / critical effect	Urinary tract (kidneys, bladder, ureters).
Lowest relevant oral NOAEL / NOEL	xxx mg/kg bw/day (NOEL, 90-day dog)
Lowest relevant dermal NOAEL / NOEL	x,xxx mg/kg bw/day (NOEL, 28-day, rat)
Lowest relevant inhalation NOAEL / NOEL	not done

Genotoxicity (OECD data point number IIA 5.4)

Ames (<i>S. typh.</i>)	negative.
HGPRT (CHO)	negative.
CA (CHL)	positive (-S9).
CA (human lymphocytes)	negative.
Mouse micronucleus	negative

Long term toxicity and carcinogenicity (OECD data point number IIA 5.5)

Target/critical effect	Kidney, urinary bladder and ureters.
Lowest relevant NOAEL / NOEL	NOEL (rat study); xx – xx mg/kg bw/day
Carcinogenicity	Rat: Transitional cell carcinoma (1 incidence), papilloma (1 incidence) in females at xxxx ppm (xxx mg/kg bw/day), NOEL = xxx ppm (xx - xx mg/kg bw/day). Mice: Increased incidence of mesenchymal tumours in males at > xxxx ppm (xxx mg/kg bw/day) induced by epithelial irritation. NOEL = xxx ppm (xx mg/kg bw/day).

Reproductive and developmental toxicity (OECD data point number IIA 5.6)

Reproduction target / critical effect	Body weight effects and urinary system pathology.
Lowest relevant reproductive NOAEL / NOEL	x,xxx ppm (xx,xxx- xxx mg/kg bw/day). Systemic NOEL = xxxx ppm (xxx –xxx mg/kg bw/day)
Developmental target / critical effect	Rat: None seen. Rabbit: None seen.
Lowest relevant developmental NOAEL / NOEL	Rat: > x,xxx mg/kg bw/day. Rabbit: > x,xxx mg/kg bw/day.

Neurotoxicity / delayed neurotoxicity (OECD data point number IIA 5.7)

Acute neurotoxicity	NOEL > x,xxx mg/kg bw
Subchronic neurotoxicity	NOEL > xx,xxx ppm (x,xxx – x,xxx mg/kg bw/day).

Other toxicological studies (OECD data points number IIA 5.8)

None

Medical data (OECD data point number IIA 5.9)

None

Summary (OECD data point IIA 5.11)

	Value	Study	Safety factor
ADI	0.xx mg/kg bw/day	Rat 2-year feeding study.	100
AOEL (short term)	x mg/kg bw/day.	90-day and one year dog studies.	100
(long term)	0.xx mg/kg bw/day	Rat 2-year feeding study.	100
Drinking water limit	x.xxx µg/L		
ARfD (acute reference dose)	Not relevant.		

Dermal absorption (OECD data points number IIA 5.9.9 & IIIA 7.6)

Not done.	No effect in rat 28 day dermal study up to xxxx mg/kg bw/day.
--------------------	---

Chemco	September 1997	Chemx (proposed ISO name)	page of
--------	----------------	---------------------------	---------

Chapter 4: Residues

Metabolism in plants (OECD data point numbers IIA 6.2.1, IIA 6.7, IIIA 8.2 and IIIA 8.7)

Plant groups covered	Wheat.
Rotational crops	Lettuce, radish, barley, rye, sugar beet, winter barley, field beans/peas, triticale, maize and vetch. Data indicates that sugar beet cannot be planted in soil within 1 year of chemx being applied to crops in that soil at 20 g as/ha.
Plant residue definition for monitoring	“the sum of chemx and its ethylsulfone metabolites which can be hydrolysed to metabolite 7, expressed as chemx”
Plant residue definition for risk assessment	“the sum of chemx and its ethylsulfone metabolites which can be hydrolysed to metabolite 7, expressed as chemx”
Conversion factor (monitoring to risk assessment)	None

Metabolism in livestock (OECD data point numbers IIA 6.2.2 to IIA 6.2.5, IIA 6.7, IIIA 8.4 and IIIA 8.7)

Animals covered	Lactating ruminants (goats) and poultry
Animal residue definition for monitoring	“the sum of chemx and its ethylsulfone metabolites which can be hydrolysed to metabolite 7, expressed as chemx”
Animal residue definition for risk assessment	“the sum of chemx and its ethylsulfone metabolites which can be hydrolysed to metabolite 7, expressed as chemx”
Conversion factor (monitoring to risk assessment)	None
Metabolism in rat and ruminant similar (yes/no)	Yes
Fat soluble residue: (yes/no)	No

Residues in succeeding crops (OECD data point numbers IIA 6.6 and IIIA 8.6)

.....	Whereas residues can be detected in following crops it is unlikely that the residues will exceed the LOQ as proposed
-------	--

Stability of residues (OECD data point numbers IIA 6.1 and IIIA 8.1)

.....	Residues were stable for the duration of the residue trials as carried out.
-------	---

Residues from livestock feeding studies (OECD data point number IIA 6.4 and IIIA 8.4)

Intakes by livestock \geq 0.1 mg/kg diet/day:		Ruminant: yes/no	Poultry: yes/no	Pig: yes/no
Muscle	Data was not required			
Liver	Data was not required			
Kidney	Data was not required			
Fat	Data was not required			
Milk	Data was not required			
Eggs	Data was not required			

Consumer risk assessment (OECD data point number IIA 6.9 and IIIA 8.10)

ADI	0.xx mg/kg bw/day.
TMDI (% ADI)	0.11 %
NEDI (% ADI)	Not required
Factors included in NEDI	No factor used
ARfD	Not relevant
Acute exposure (% ARfD)	Not relevant

Processing factors (OECD data point number IIA 6.5 and IIIA 8.5)

Crop/processed crop	Number of studies	Transfer factor	% Transference
No data required			

Proposed MRLs (OECD data point number IIA 6.7.2 and IIIA 8.7.2)

Wheat grain.....	0.02* mg/kg
All other crops.	0.02* mg/kg

* at or about the limit of quantification

Summary of critical residues data (OECD data point numbers IIA 6.3 and IIIA 8.3)

Crop	Country and / or Region	Trials results relevant to the critical GAP (a)	Recommendation/comments	MRL	STMR (b)
Wheat	European Union – northern region	8 x < 0.01mg/kg	No residues are expected in wheat grain.	0.02 mg/kg	Not relevant.
Wheat	European Union – Mediterranean region	4 x < 0.01 mg/kg	No residues are expected in wheat grain.	0.02 mg/kg.	Not relevant.

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17

(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the critical GAP

Chapter 5: Fate and behaviour in the environment

Route of degradation (aerobic) in soil (OECD data point number IIA 7.1.1)

Mineralization after 100 days	1.6% (2.2% at 225d) chem2 ¹⁴ C	8.1% (13% at 225d) chem3 ¹⁴ C
Non-extractable residues after 100 days	14% (41% at 225d)	15% (33% at 225d)
Relevant metabolites ³⁰ - name and/or code, % of applied (range and maximum)	xxxxxxx (metabolite 2) 2.2-9.1% (15% at 225d)	
	desmethyl 1.0-28.0% (19% at 225d)	0.9-29.0% (19% at 225d)
	metabolite 3 -	0.9-3.4% (1.8% at 225d)

Route of degradation in soil - supplemental studies (OECD data point numbers IIA 7.1.2 and IIA 7.1.3)

Anaerobic degradation	No data presented	
Soil photolysis	DT ₅₀ sunlight 46 d chem2 ¹⁴ C	51 d chem3 ¹⁴ C
	DT ₅₀ darkness 55 d chem2 ¹⁴ C	117 d chem3 ¹⁴ C
	xxxxxxx (metabolite 2) 22.6%	-
	Metabolite 3 -	24.9%

Rate of degradation in soil (OECD data point numbers IIA 7.2, IIA 7.3, IIIA 9.1 and IIIA 9.2)

Method of calculation	Method of Calculation	
Laboratory studies (range or median, with n value, with r ² value)	DT _{50lab} (20°C, aerobic):	
	Speyer 2.2 soil 51-54d (n=6) r ² =0.996/0.988	Pseudo first order kinetics
	UK soils 92-226d (n=8) r ² =0.972/0.994	Gustafson & Holden 1990
	US soils (25°C) 31-37d (n=12)	
	US soils (25°C) 74-88d (n=12)	
	DT _{90lab} (20°C, aerobic):	
	Speyer 2.2 soil 170-181d (n=6) r ² =0.996/0.988	Pseudo first order kinetics
	UK soils 306-750d (n=8) r ² =0.972/0.994	Gustafson & Holden 1990
	US soils (25°C) 206-262d (n=12)	
	DT _{50lab} (10°C, aerobic):	
UK soil > 365d (n=8)	Pseudo first order kinetics	
DT _{50lab} (20°C, anaerobic): No data presented		
Degradation in the saturated zone: No data, residues not Expected to reach this zone.		
Field studies (state location, range or median with n value)	DT _{50f} :	
	Belgium/France/Germany/UK 11-47d (n=10)	Timme, Frehse & Laska 1992
	Canada/Saskatchewan/Alberta 13-52d (n=8)	Gustafson & Holden 1990
	DT _{90f} :	
Belgium/France/Germany/UK 131-358d (n=10)	Timme, Frehse & Laska 1992	
Canada/Saskatchewan/Alberta 370-1190d (n=8)	Gustafson & Holden 1990	

³⁰ An internationally agreed definition of the term *relevant metabolites* has not been elaborated. Pending the development of such a definition, applicants should consult the regulatory authority of the country to which application is to be made, for guidance concerning selection of the metabolites for which information must be reported

Chemco	September 1997	Chemx (proposed ISO name)	page of
--------	----------------	---------------------------	---------

Soil accumulation and plateau concentration

No data presented. No evidence of accumulation in field studies at recommended use rate:
 Chemx residues < 0.0005 - 0.0007 mg/kg after one year
 Xxxxxxxx (metabolite 2) / desmethyl chemx residues < 0.0005 - 0.0013 mg/kg after one year (0-20 cm)
Metabolite 3 residues
 Canadian soils (0 – 15 cm) 0.009 mg/kg after one year [bare soil treated with 136 g as/ha]
 US soils (0-15 cm) 0.006 mg/kg after one year [bare soil treated with 70 g as/ha]

Soil adsorption/desorption (OECD data point numbers IIA 7.4.1 and IIA 7.4.2)

Koc

K_f /K_{oc}

K_d

pH dependence (yes / no) (if yes type of dependence)

Chemx	5.3 - 89.0
Xxxxxxxx (metabolite 2)	60.9 - 260.5
Desmethyl chemx	36.7 - 116.0
Metabolite 3	259.9 - 8279.9
Chemx adsorption increases with decreasing soil pH	

Mobility in soil (OECD data point numbers IIA 7.4.3 – IIA 7.4.8 and IIIA 9.3.1 – IIIA 9.3.3)

Column leaching

Aged residues leaching

No data presented.		
	Column leachate	Soil section (0-5 cm)
Applied radioactivity	30 – 39 %	47-49%
Chemx	25 – 39 %	19-23%
Xxxxxxxx (metabolite 2)	< 2 %	< 1 %
Desmethylchemx	c. 2 %	c.1 %
xxx (metabolite 10)	< 2 %	< 1 %
Metabolite 3	< 2 %	< 1 %
Unknown	c. 3 %	< 1 %

Lysimeter/ field leaching studies

3-year field lysimeter study. Single and successive treatment at 1.5 times recommended rate (30 g as/ha). Precipitation c.1000 mm/year. Leachate recovery c.8 % of applied radioactivity. Chemx and twelve radioactive fractions detected in leachate.
 Radioactive leachate fractions detected (µg parent equivalents/L)

Application	Single		Successive		
	Monthly	Yearly	Monthly	Yearly	
Fraction	Year	Peak	Mean	Peak	Mean
Chemx	1	0.01	<0.01	0.06	0.02
	2	0.02	<0.01	0.05	0.03
	3	nd	nd	0.03	0.01
	Total		<0.01		0.02

Appendix 10 Format for the Compilation of Tier III Overall Summaries and Assessments – List of end points

Chemco	September 1997	Chemx (proposed ISO name)	page	of
--------	----------------	---------------------------	------	----

Application	Year	Single		Successive	
		Monthly Peak	Yearly Mean	Monthly Peak	Yearly Mean
M1	1	nd	nd	nd	nd
	2	0.02	<0.01	0.06	0.02
	3	0.02	<0.01	0.03	0.01
	Total		<0.01		0.01
M2	1	0.06	0.02	0.09	0.04
	2	0.06	0.02	0.10	0.06
	3	0.05	0.02	0.07	0.03
	Total		0.02		0.04
M3	1	nd	nd	0.13	0.02
	2	0.02	<0.01	0.14	0.06
	3	0.02	0.01	0.08	0.04
	Total		<0.01		0.04
M4	1	nd	nd	0.03	<0.01
	2	nd	nd	nd	nd
	3	nd	nd	0.04	0.01
	Total		nd		<0.01
M5	1	0.04	0.01	0.14	0.02
	2	0.09	0.06	0.17	0.10
	3	0.04	0.02	0.18	0.10
	Total		0.03		0.07
M6	1	0.07	0.02	0.09	0.03
	2	0.02	0.01	0.36	0.11
	3	0.01	<0.01	0.02	0.01
	Total		0.01		0.05
M7	1	0.08	0.04	0.04	0.02
	2	0.16	0.12	0.15	0.08
	3	0.15	0.12	0.18	0.13
	Total		0.09		0.07
M8	1	0.12	0.05	0.14	0.04
	2	0.06	0.03	0.63	0.20
	3	0.01	<0.01	0.05	0.03
	Total		0.03		0.09
M9	1	0.01	<0.01	0.01	0.00
	2	0.01	<0.01	0.02	0.01
	3	0.01	<0.01	0.02	0.01
	Total		<0.01		0.01
M10, M11 & M12	1		≤0.01		≤0.01
	2		≤0.01		≤0.01
	3		≤0.01		≤0.01
	Total		≤0.01		≤0.01

Chemco September 1997 Chemx (proposed ISO name) page of

Chemx was detected at a maximum mean annual concentration of <0.01 µg/L after a single application and 0.3 µg/L after successive applications of 30 g as/ha. Of the major soil metabolites only xxxxxxx (metabolite 2) was detected at levels ≤ 0.02 µg/L, desmethyl chemx and metabolite 3 were not detected. Four other radioactive components were detected at mean annual concentration levels at or above 0.1 µg/L, M5 0.10 µg/L, M6 0.11 µg/L, M7 0.13 µg/L and M8 0.20 µg/L. When these concentrations are adjusted for the recommended use rate of 20 g as/ha, it may be assumed that the amount leached will reduce accordingly – M5 0.067 µg/L, M6 0.073 µg/L, M7 0.087 µg/L, M8 0.13µg/L.

Of these major detectable moieties the only component characterised in field testing was M7 which comprised < 2 % of applied radioactivity 360 days post application. The M8 component was unusual in that four successive untypical recordings in year two from September to November comprising 0.63, 0.47, 0.26 and 0.22 µg/L respectively were mainly responsible for the highest yearly mean of 0.20 µg/L in the leachate. These may be outlier values. When cognisance is taken of the proportionality of the leachate concentrations expected from the recommended maximum use rate it is apparent that individually they are ≤ 0.1 µg/L and collectively comprise < 0.5 µg/L. In field studies it was also demonstrated that neither chemx nor its major soil metabolites were found in significant amounts below the plough layer.

PEC (soil) (OECD data point number IIIA 9.4)

Method of calculation	Herrchen 1996
Application rate	0.020 kg as/ha

PEC _(s) mg as/kg soil	Single application	Single Application	Multiple Application	Multiple application
	Actual	Time weighted average	Actual	Time weighted average
Initial	x.xxxx			
Short term 24h		x.xxxx		
2d		x.xxxx		
4d		x.xxxx		
Long term 7d	x.xxxx – x.xxxx			
(0-10 cm) 28d	x.xxxx – x.xxxx			
50d	x.xxxx – x.xxxx			
100d	x.xxxx – x.xxxx			

Chemco	September 1997	Chemx (proposed ISO name)	page of
--------	----------------	---------------------------	---------

Route and rate of degradation in water (OECD data point numbers IIA 2.9 & IIA 7.5 to IIA 7.9)

	chem2 ¹⁴ C	chem3 ¹⁴ C	
Hydrolysis of active substance and relevant metabolites ³⁰ (DT ₅₀) (state pH and temperature) (25°C)	pH4: 7 d	93 %	
	pH5: 48 d	34 %	
	pH7: 168 d	13 %	
	pH9: 156 d	15 %	
Photolytic degradation of active substance and relevant metabolites ³⁰	Photolytic Degradation		
		chem2 ¹⁴ C	chem3 ¹⁴ C
	pH 7.0 Buffer (25°C)		
	DT ₅₀ (hours)	36.3	33.0
	Metabolite 3	-	28.31 %
	xxxx (metabolite 9)	-	20.95 %
	N-hydroxy (metabolite 12)	-	14.98 %
	Metabolite 8	28.34 %	-
	xyxx (metabolite 5)	14.59 %	-
	xyyx (metabolite 10)	15.62 %	-
Readily biodegradable (yes/no)	No data presented.		
Degradation in water/sediment (20°C)	- DT ₅₀ water	16.1 – 19.5 d	
	- DT ₉₀ water	83.9 – 101.8 d	
	- DT ₅₀ whole system	19.8 – 32.2 d	
	- DT ₉₀ whole system	103.5 – 107.0 d	
Mineralisation			
Non-extractable residues			
Distribution in water / sediment systems (active substance)	11.3 - 11.8 % (100 d)		
Distribution in water / sediment systems (metabolites) ³⁰	desmethylchemx	12.9 - 14.0 % (30 d)	
	xxxxxxx (metabolite 2)	5.3 - 6.1 % (100 d)	
	metabolite 3	1.4 - 1.7 % (30/60 d)	
	Unidentified	10.8 - 14.1 % (14 d)	

PEC (surface water) (OECD data point numbers IIIA 9.8.1 – IIIA 9.8.6)

Method of calculation	Herrchen 1996
Application rate	0.020 kg as/Ha
Main routes of entry	Spray Drift - Run Off

Appendix 10 Format for the Compilation of Tier III Overall Summaries and Assessments – List of end points

Chemco September 1997 Chemx (proposed ISO name) page of

PEC _(sw) µg as/L	Single application	Single Application		Multiple Application	Multiple application
	Actual	Time weighted average		Actual	Time weighted average
Initial	0.04 - 0.27	Drift	Run Off		
Short term 24h		0.0398	0.0497		
2d		-	-		
4d		0.0391	0.0488		
Long term 7d		0.0384	0.0480		
14d		0.0370	0.0460		
21d		-	-		
28d		0.0354	0.0442		
42d		0.0340	0.0425		

PEC (sediment)

Method of calculation

Spray drift contamination (4 %)

First order DT₅₀ 33 days. STD density (0-5 cm) 0.020 kg as/ha

Application rate

PEC _(sed) µg/kg	Single application	Single Application		Multiple Application	Multiple application
	Actual	Time weighted average		Actual	Time weighted average
Initial	0.19	0.19			
Short term	0.18	0.19			
Long term	0.12	0.15			

PEC (ground water) (OECD data point numbers IIIA 9.6.1 and IIIA 9.6.2)

Method of calculation and type of study (e.g. modelling, monitoring, lysimeter)

3-year Lysimeter study

Application rate

0.030 kg as/ha

Chemco	September 1997	Chemx (proposed ISO name)	page of
--------	----------------	---------------------------	---------

PEC_(gw)

3-year results (µg parent equivalents/L)

Maximum concentration

Max. conc	Single Application	Successive Applications
Moiety		
chemx	0.01 - 0.02	0.03 - 0.06
M1	< 0.01 - 0.02	0.03 - 0.06
M2	0.05 - 0.06	0.07 - 0.10
M3	< 0.01 - 0.02	0.08 - 0.14
M4	< 0.01	< 0.01 - 0.04
M5	0.04 - 0.09	0.14 - 0.18
M6	0.01 - 0.07	0.02 - 0.36
M7	0.08 - 0.16	0.04 - 0.18
M8	0.01 - 0.12	0.05 - 0.63
M9	0.01	0.01 - 0.02

Average annual concentration

Av. Ann. Conc.		
Chemx	< 0.01	0.01 - 0.03
M1	< 0.01	0.01 - 0.02
M2	0.02	0.03 - 0.06
M3	< 0.01 - 0.01	0.02 - 0.06
M4	< 0.01	< 0.01 - 0.01
M5	0.01 - 0.06	0.02 - 0.10
M6	< 0.01 - 0.02	0.01 - 0.11
M7	0.04 - 0.12	0.02 - 0.13
M8	< 0.01 - 0.05	0.03 - 0.20
M9	0.01	0.01

Fate and behaviour in air (OECD data point numbers IIA 7.10 and IIIA 9.9)

Direct photolysis in air

Low Vapour Pressure: 3.05×10^{-8} Pa (20°C)

Quantum yield of direct phototransformation at $\lambda > 290$ nm

$\Phi = 1.81 \times 10^{-3}$

Photochemical oxidative degradation in air

Latitude:	Season:	DT ₅₀
Henry's Law Constant:		8.15×10^{-7} Pa/m ³ /mol (pH5)
		8.83×10^{-9} Pa/m ³ /mol (pH7)
		2.97×10^{-8} Pa/m ³ /mol (pH9)

Volatilization

from plant surfaces:

from soil:

Appendix 10 Format for the Compilation of Tier III Overall Summaries and Assessments – List of end points

Chemco	September 1997	Chemx (proposed ISO name)	page of
--------	----------------	---------------------------	---------

PEC (air)

Method of calculation	No data presented.
-----------------------	--------------------

PEC_(a)

Maximum concentration	No data presented
-----------------------	-------------------

Definition of the Residue (OECD data point number IIA 7.11)

Relevant to the environment	Chemx parent equivalent, determined as the ethylsulfone metabolite (metabolite 7), expressed as chemx
-----------------------------	---

Monitoring data, if available (OECD data point number IIA 7.12)

Soil (indicate location and type of study)	No data presented
Surface water (indicate location and type of study)	No data presented
Ground water (indicate location and type of study)	No data presented
Air (indicate location and type of study)	No data presented

Chapter 6: Effects on non-target species

Effects on terrestrial vertebrates (OECD data point numbers IIA 8.1, IIIA 10.1 and IIIA 10.3)

Acute toxicity to mammals	Rat - Oral LD ₅₀ > 5000 mg as/kg bw
Acute toxicity to birds	Bobwhite Quail / Mallard Duck LD ₅₀ > xxxx mg as/kg bw
Dietary toxicity to birds	Bobwhite Quail / Mallard Duck LC ₅₀ > xxxx mg as/kg diet
Reproductive toxicity to birds	Mallard Duck NOEC xxx mg as/kg diet
Chronic toxicity to mammals	Rat NOEL xx mg as/kg bw/day

Toxicity/exposure ratios for terrestrial vertebrates (OECD data point numbers IIIA 10.1.1, IIIA 10.1.2 and IIIA 10.3.1)

Application rate (kg as/ha)	Crop	Category (e.g. insectivorous bird)	Time-scale	TER	TER risk assessment trigger *
0.020	Short grass	Grazing bird	Acute	xxxx	< 10
			Short term	xxxx	< 10
			Long term	xxx	< 5
	Small insects	Insectivorous bird	Acute	xxxxx	< 10
			Short term	xxxx	< 10
			Long term	xxx	< 5
	Large insects	Insectivorous bird	Acute	xxxxx	< 10
			Long term	xxxx	< 5
			Short grass	Small mammal	Acute
			Long term	xx	< 5
	Short grass	Large mammal	Acute	xxxxx	< 10
			Long term	xxx	< 5

* in the EU a risk assessment must be carried out relevant to practical conditions of use where the TER values reported are less than these values

Toxicity data for aquatic species (most sensitive species of each group) (OECD data point numbers IIA 8.2 – IIA 8.6 and IIIA 10.2.2 – IIIA 10.2.7)

Group	Test substance	Time-scale	Endpoint	Toxicity (mg/L)
Laboratory tests				
Fish species	> 98.5% as	96 hour	LC ₅₀	> xx
		87 day	NOEC	Xxx
Invertebrate species	> 98.5% as	48 hour	LC ₅₀	> xx
		21 day	NOEC	Xxx
Algal species	> 98.5% as	72 hour	EC ₅₀	x.xxx
		72 hour	EC ₅₀	x.x1
Aquatic plants	> 98.5% as	14 day	IC ₅₀	x.xxx
Lemna 14 day toxicity study with recovery phase	14 day IC ₅₀ c.x.xx µg as/L. No significant effect at x.x µg as/L over 7 days exposure. Recovery within 6-9 days after 4 days exposure to x.x µg as/L. For the main metabolite - desmethyl chemx (determined in water) no significant effect on Lemna following 7 days exposure to xx.x µg as/L.			

Toxicity/exposure ratios for the most sensitive aquatic organisms (OECD data point numbers IIIA 10.2.1)

Application rate(kg as/ha)	Crop	Organism	Time-scale	Distance (m)	TER	TER risk assessment trigger *
0.020	Cereals	<i>Cyprinus carpio</i>	Acute	1	xx.x x 10 ⁴	< 100
		<i>Oncorhynchus</i>	Long term	5	xxx.x x 10 ⁴	< 10
		<i>Daphnia magna</i>	Acute	1	xx.x x 10 ⁴	< 100
		<i>Daphnia magna</i>	Long term	5	xxx.x x 10 ⁴	< 10
		<i>Selenastrum</i>	Acute	1	xxx.x	< 10
		<i>Scenedesmus</i>	Acute	1	x.x x 10 ⁴	< 10
		<i>Lemna gibba</i>	Acute	1	x.	< 10
			Short term	5	xx	< 10

* in the EU a risk assessment must be carried out relevant to practical conditions of use where the TER values reported are less than these values

Bioconcentration

No fish bioconcentration study presented

Bioconcentration factor (BCF)

Risk assessment trigger (practical conditions of use) for the bioconcentration factor *

Clearance time (CT₅₀)
(CT₉₀)

Level of residues (%) in organisms after the 14 day depuration phase

Log P _{ow} chemx < 1 (pH 5 - 9)
BCF > 1000 (Log P _{ow} ≥ 3)

* in the EU a risk assessment must be carried out relevant to practical conditions of use where the BCF value reported is greater than this value

Appendix 10 Format for the Compilation of Tier III Overall Summaries and Assessments – List of end points

Chemco September 1997 Chemx (proposed ISO name) page of

Effects on honeybees (OECD data point numbers IIA 8.7 and IIIA 10.4.2 – IIIA 10.4.7)

Acute oral toxicity	48 Hour Oral LD ₅₀ > 30 µg as/bee
Acute contact toxicity	48 Hour Dermal LD ₅₀ > 25 µg as/bee

Hazard quotients for honey bees (OECD data point number IIIA 10.4.1)

Application rate (kg as/ha)	Crop	Route	Hazard quotient	Hazard quotient risk assessment trigger *
Laboratory tests				
0.020	Cereals	Oral	< x.xx	> 50
		Contact	< x.xx	> 50

* in the EU a risk assessment must be carried out relevant to practical conditions of use where the hazard quotients reported are greater than these values

Field or semi-field tests
No extended tests presented.

Effects on other arthropod species (OECD data point numbers IIA 8.8.1, IIA 8.8.2 and IIIA 10.5)

Species	Stage	Test Substance	Dose (kg as/ha)	Endpoint	Effect	Risk assessment trigger *
Laboratory tests						
<i>B. tetracolum</i>	Adult	OEC 2222	0.0303	Survival	Nil	> 30 %
<i>Pardosa spp.</i>	Adult	OEC 2222	0.0303	Food consumption	Nil	> 30 %
<i>Typh. pyri</i>	Protonymph	OEC 2222	0.0297	Survival	< 30 %	> 30 %
<i>Aphidius</i>	Adult	OEC 2222	0.0297	Fecundity	c.7 %	> 30 %
Field or semi-field tests						
No semi-field data presented.						

* in the EU a risk assessment must be carried out relevant to practical conditions of use where the effects reported are greater than these values

Effects on earthworms (OECD data point numbers IIA 8.9 and IIIA 10.6.2 – IIIA 10.6.7)

Acute toxicity	14 day LC ₅₀ > xxx mg as/kg soil
Reproductive toxicity	56 day NOEC ≥ x.xx mg as/kg soil

Toxicity/exposure ratios for earthworms (OECD data point number IIIA 10.6.1)

Application rate (kg as/ha)	Crop	Time-scale	TER	TER risk assessment trigger *
0.020	Cereals	Acute	xxxxx	< 10
		Long term	xx	< 5

* in the EU a risk assessment must be carried out relevant to practical conditions of use where the TER values reported are less than these values

Chemco	September 1997	Chemx (proposed ISO name)	page of
--------	----------------	---------------------------	---------

Effects on soil micro-organisms (OECD data point numbers IIA 8.10 and IIIA 10.7)

Nitrogen mineralization

2 soil types treated with 1.5 and 5.76 times recommended field rate, and assessed over a 100 day period.

No significant adverse effect on either soil biomass or mineral nitrogen level at the low rate in either sandy loam or loamy sand soil or at the five fold rate in the sandy loam soil.

In the loamy sand soil at five fold rate a transient effect on soil microflora was observed with subsequent recovery to normal levels.

Carbon mineralization