PART 4

Section 4 Residues in or on Treated Products, Food and Feed

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

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

IIA 6.1.1 Stability of residues during storage of samples

Report: IIA 6.1.1/01 Black A 1996, Stability of chemx in wheat raw agricultural commodities during storage, Report No.: CC-14394

Guidelines

US EPA 40 Guideline CFR Part 160 and European Commission Guideline, Appendix H (Document 7032/VI/95), but with the following exception - only single sample analyses were performed at each interval, rather than two as recommended in the EU guideline.

GLP: Fully GLP compliant [17]

Executive Summary

In freezer storage stability studies, samples of ground wheat grain and forage were spiked with chemx (98 % and 99 % purity) at a level of 0.2 mg/kg and stored at -12°C (10°F) for 531 to 533 days (18 months). Samples were analyzed using a common moiety method of analysis, a method that determines parent chemx and its ethylsulfone metabolites. Results are expressed in terms of chemx parent equivalent. 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.

Under the conditions of the study, total residues decreased by 11% and 10% in grain and forage respectively. The data reported indicate that total residues of chemx were stable at -12ºC (10ºF) in grain and forage.

I. MATERIALS AND METHODS

A. MATERIALS

1. **Test Materials:** Chemx
   Description: White powder
   Lot/Batch #: NPD-9301-4706-T [18]
   NPD-9211-4628-T [18]

Purity: 98 % (NPD-9301-4706-T) and 99 % (NPD-9211-4628-T)
CAS # : 16335-17-2
Development code: CR 48500
Spiking levels: 0.2 mg / kg

2. Test Commodity:

Crop: Wheat
Type: Winter
Variety: Rambo
Botanical name: *Triticum aestivum*
Crop parts(s) or processed commodity: untreated grain; wheat forage
Sample size: 10.0 ± 1 g

B. STUDY DESIGN

The study was conducted during the period February 1995 to September 1996 by the Chemco Research Laboratory, New York.

1. Test procedure

Duplicate test samples were fortified at eight time points over a period of 533 days for grain and 531 days for forage during which they were kept in a in a frozen condition (< - 12°C) pending analysis. At the conclusion of the storage period, all samples were analysed for chemx residues using the same analytical method as that employed for crop residue studies.

2. Description of analytical procedures

The method of analysis used in the study involved hydrolysis of parent chemx and its metabolites to a common target analyte, an ethylsulphone derivative, a method which does not distinguish between parent chemx and its metabolites for the purposes of quantifying residues. The method does not provide information as to the true stability of parent chemx. It does however permit the stability of the sum of the sulphone generating precursor compounds that are present in the sample to be assessed (*i.e.* the compounds included in the proposed residue definition).

II. RESULTS AND DISCUSSION

The data indicate that when frozen samples of grain and forage, intended for residue analyses, are stored for extended periods of up to 533 days, acceptable stability can be expected (Table IIA 6.1.1-1).

Table IIA 6.1.1-1 Stability of chemx residues in winter wheat grain and forage following storage at < 12°C

Winter Wheat grain		Winter Wheat forage	
Days of storage	% recovery	Days of storage	% recovery
0	96.67	0	90.13
113	91.59	111	80.2
168	93.61	166	79.39
225	91.36	223	96.81
281	93.18	279	84.01
352	90.02	350	97.31
434	87.85	432	79.34
533	85.21	531	79.97

III. CONCLUSIONS

Chemx residues in wheat grain and forage are stable for periods of storage at < - 12°C of up to 533 days, a period which exceeds the longest time period for which samples were stored in the course of the residue trial studies.

(Black A 1996)

IIA 6.2.1 Metabolism, distribution and expression of residues in plants

IIA 6.2.1.1 Metabolism, distribution and expression of residues in wheat

Report: IIA 6.2.1/01 - Green RG 1994, Metabolism of chemx in wheat, 1994, Chemco Report XX-13043

Guideline

EPA Pesticide Assessment Guideline 171-4 (a), Nature of the Residue in Plants: Subdivision O, Residue Chemistry. The report also meets the requirements of EU Directive 91/414/EEC, Annex II, point 6.1.

GLP: Fully GLP compliant [17].

Executive Summary

In a metabolism study in wheat, a simulated WG formulation of chemx (chem2ring 98 % and 99.7 radiochemical purity, chem3ring 99.4 and 99.9 % radiochemical purity, labelled with ^{14}C at the C-3 and C-5 positions respectively) was applied pre-emergence and post emergence at 70 g as/ha and 200 g as/ha (3.5 times and 10 times the recommended label rate). In the post emergence application chemx was applied at crop growth stage 3 (Feekes scale) using a manual sprayer, samples of foliage were collected 2 weeks after treatment and samples of mature plants were collected 10 weeks after the post emergence treatment and were separated into grain and straw. Residues were highest in foliage and straw and were just quantifiable in grain with the analytical method used.

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.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Chemx -

chem2 ring labelled: ^{14}C in the C-3 position; specific activity 28.6 mCi/mmol for both post-emergence and pre-emergence treatments;

chem3 ring labelled: ^{14}C in the C-5 position; specific activity 29.1 mCi/mmol in the case of post-emergence treatments and 29.4 mCi/mmol in the case of pre-emergence treatments

Description: White powder

Purity: chem2 ring labelled: radiochemical purity ≥ 98.0 % post-emergence; ≥ 99.7 % pre-emergence

chem3 ring labelled: radiochemical purity ≥ 99.4 % post-emergence; ≥ 99.9 % pre-emergence

CAS #: 16335-17-2

Stability of test compound: The test material was stable for at least 7 days at room temperature.

2. Soil: An elder loamy sandy was used.

Table IIA 6.2.1-1 Soil Physicochemical Properties

Soil Series	Soil Type	pH	OM %	Sand %	Silt %	Clay %	Moisture holding capacity (at 1/3 bar)	CEC meg / 100g
Elder	Loamy Sand	*6.6	**1.1	78	10	12.0	9.92	10.7

* measured in a 1 : 2.5 soil : water suspension ** Organic matter calculated as 1.72 x percent organic carbon

B. STUDY DESIGN

The study was conducted during the period March 1993 to May 1994 by the Chemco Research Laboratory, New York.

1. Experimental conditions

The metabolism of chemx was investigated in wheat grown in wooden boxes (76 cm x 91 cm by 30 cm depth) filled with a sandy loam soil. The boxes were maintained in screen-houses equipped with ventilation fans and windows.

A simulated WG formulation of chemx was applied pre-emergence and post-emergence. In the case of the post emergence treatments, the test material was applied at the crop growth stage of 3 (Feekes scale), using a manual sprayer. The treatments were made at the exaggerated rates of 70 g as/ha (3.5X the recommended field use rate) and 200 g as/ha (10X the recommended field use rate) to provide sufficient radioactivity for quantification and identification or characterisation of residues.

2. Sampling

Wheat samples were collected at the foliage stage 2 weeks after treatment. Mature plants were harvested in June 1993, 10 weeks after the post-emergence treatment, and separated into grain and straw.

II. RESULTS AND DISCUSSION

A. TOTAL RADIOACTIVE RESIDUES (TRRs)

Following the application of chemx to wheat at target doses of 70 and 200g as/ha both pre-emergence (PHI ~ 104 d) and post-emergence (PHI ~ 83 d), the total ^{14}C residue [TRR] was measured in grain, forage and in straw (Table IIA 6.2.1-2).

The results indicated that ^{14}C residues occur at higher levels in forage and straw samples following post-emergence treatment than are found following pre-emergence treatment. Residues in grain are comparable for both treatment types and are just quantifiable with the analytical method used. The data indicate that if chemx is applied at the current recommended rate of 20 g as/ha [GS 13 - 39] then quantifiable residues of chemx and its metabolites should not be detectable in grain at levels greater than 0.01 mg/kg.

Residues in straw and forage for pre-emergence treated wheat are greater for chem2 labelled chemx than for chem3 labelled chemx. This suggests that metabolites containing the chem2 moiety are taken up more readily from soil than are those containing the chem2 moiety which in turn gives rise to the higher residue, a finding that may have some relevance for residue levels in rotational crops.

The mean interception rate for the plants in post-emergence applications of chemx was found to be 12.9 % of the applied dose.

B. EXTRACTION AND CHARACTERIZATION OF RESIDUES

The extractability of ^{14}C residue in grain, forage and straw was determined using an acetonitrile / water [25:75] solvent mixture (Table IIA 6.2.1-3).

Table IIA 6.2.1-2 Total radioactive residues (TRRs) in plants following pre-emergence and post-emergence application of chem2 label chemx or chem3 label chemx

TRRs (mg/kg) in treated grain, forage and straw *				
Commodity.	Chem2 labelled chemx		chem3 labelled chemx	
Target** application rate ⇒	70 g as/ha	200 g as/ha	70 g as/ha	200 g as/ha.
grain , treated post emergence	0.0027	0.0076	0.005	0.013
straw, treated post emergence	0.32	1.1	0.31	1.1
Forage, treated post emergence	0.89	2.9	0.77	1.6
grain , treated pre emergence.	0.0021	0.0044	0.0047	0.0095
straw, treated pre emergence.	0.065	0.21	0.031	0.066
Forage, treated pre emergence.	0.012	0.025	0.0046	0.01

* limit of quantification was 0.00086 mg/kg for grain, 0.0014 mg/kg for forage, 0.0018 mg/kg for straw.

** In the case of the nominal 200 g as/ha application rate the actual rates achieved were 164.5 g as/ha (pre-emergence, chem2 chemx), 185.2 g as/ha (pre-emergence, chem3 chemx), 197.6 g as/ha (post-emergence, chem2 chemx), 171.9 g as/ha (post-emergence chem3 chemx) along with two special treatments at 200.4 and 200.6 g as/ha (pre-emergence, chem2 chemx). The achieved lower rates ranged from 66 to 70.6 g as/ha for both labels.

Table IIA 6.2.1-3 Extraction efficiency for residues of chemx in grain, forage and straw

Extractability of ^{14}C residues with acetonitrile / water [25:75]						
	Grain		Forage		Straw.	
	%^{14}C extracted	% ^{14}C not extracted	%^{14}C extracted	% ^{14}C not extracted	%^{14}C extracted	% ^{14}C not extracted
Post-emergence chem2 chemx, 70g as/ha rate.	n.e.		102.3	6.9	84.2	12
Post-emergence chem2 chemx, 197.6g as/ha rate.	39.8	59.6	93.7	6.3	86.7	10.3 [6.2 *]
Post-emergence chem3 chemx, 70 g as/ha rate.			98.9	7.3	81.4	16.5 [11.8 *]
Post-emergence chem3 chemx, 171.9g as/ha rate.	38.4	61.5	93.2	6.8	76.8	14.7 [10.8*]
Pre-emergence chem2 chemx, 70 g as/ha rate.	n.e.		n.e.		78.8	15.8
Pre-emergence chem2 chemx, 164.5g as/ha rate.	61.1	37.6	77.5	15.6	73.2	13.9
Pre-emergence chem3 chemx, 70 g as/ha rate.	n.e.		n.e.		63.6	24.7
Pre-emergence chem3 chemx , 185.2 g as/ha rate.	26.2	77.4	73.6	29.3	62.5	24.9

n.e. not extracted ** In the case of the ^{14}C not extractable in acetonitrile / water the % in [ ] is soxhlet extractable using water as solvent.

1. Extraction and characterization of residues in grain

In the case of grain the level of residues present was extremely low (Table IIA 6.2.1-2). As a consequence the characterisation of residues was limited to an evaluation of the character of extractable residues in the high application studies. Following application of 200 g as ha, extractable residues in grain ranged from 0.0024 - 0.005 mg/kg for both chem2 labelled chemx and chem3 labelled chemx. Partitioning of the extractable residue between ethyl acetate and water, at pH 7 and pH 1, resulted in 70 - 80 % of the residue at neutral pH and 74 - 100 % of the residue at pH 1 remaining in the aqueous phase. Hydrolysis of the chem2 extractable residue from post-emergence and pre-emergence applications at pH 1 and at 150°C resulted in the release of the sulphone metabolite (11 % and 33 % respectively of the ^{14}C hydrolysate), confirming the presence of metabolites containing the intact chem2 moiety. There was insufficient ^{14}C to process the chem3 labelled chemx fraction further.

Some 68 - 85 % of the non-extractable ^{14}C contained in the extracted grain was released when treated with α-amylase. It was not possible to identify any of the released ^{14}C containing metabolites (as glucose or otherwise] so it is not clear if the ^{14}C containing metabolites were entrained in or incorporated into the starch molecules present in the grain.

2. Extraction and characterization of residues in straw

In the case of straw (pre-emergence and post-emergence treatments) the total ^{14}C residues resulting from post-emergence treatments were far greater than that in the case of those resulting from pre-emergence treatments - 5 to 17 times lower (Table IIA 6.2.1-2). On the basis of a comparison of the HPLC LSC chromatograms for pre-emergence and post-emergence treatment extracts, it is clear that while the relative concentrations of the different chromatographic fractions differ, the same component peaks appear to be present. The most obvious difference between the chromatographic patterns of pre-emergence and post-emergence treatment extracts is that following post-emergence treatment with chemx the concentration of parent chemx is far higher than in extracts from pre-emergence treatments, while in extracts from pre-emergence treatments the metabolites chem2-4 and chem2-7, chem3-1, chem3-4 and chem3-6 are present at higher concentrations than in extracts from post-emergence treatments and chem2 labelled metabolites are present in greater concentrations than those of the chem3 labelled metabolites indicating a high level of uptake of chem2 labelled soil metabolites when chemx is applied pre emergence.

The presence of more polar compounds in samples from pre-emergence treatments in comparison to samples from post-emergence treatments was confirmed when extracted ^{14}C residues were partitioned between ethyl acetate and water at pH 7 and pH 1. 39.6 - 65.2 % of the residue in samples following post-emergence treatment partitioning into the aqueous phase, while in the case of samples from pre-emergence treatments, 60.4 - 96.9 % of the residue partitioned to the aqueous layer.

3. Storage stability of residues

^{14}C-Residues in samples of forage and straw were extracted and initially analyzed by HPLC within 40 days of harvest. All analyses of ^{14}C-residues in forage and grain/straw were completed within 5.6 and ~11 months, respectively. In order to assess the storage stability of ^{14}C-residues in frozen wheat samples, residues in selected samples of forage and straw from both chem2 labelled and chem3 labelled chemx treated plants were extracted and analyzed by HPLC, twice. Samples of forage were analyzed initially after 1 month of storage and again after 5.5 months of storage. Samples of straw were analyzed initially after 1.3 months of storage and again after 3.2 months of storage.

The extractability of ^{14}C-residues from each forage and straw sample was similar for both analyses, and the HPLC chromatograms of each analysis showed similar qualitative and quantitative patterns of metabolite distribution from the two storage intervals.

4. Identity of residues in straw

The identity of the residue in wheat following application of chemx was determined by analyses of samples of straw following post-emergence applications (Table IIA 6.2.1-4) - since the proposed GAP for chemx is restricted to post-emergence treatments, it is considered that metabolites present following such treatment are the most relevant for the purposes of the proposed residue definition.

The acetonitrile / water extracted straw was further examined with a view to determining the nature of the unextracted ^{14}C residue. Post-emergence chem2 label chemx treated (200 g as/ha) and chem3 label chemx treated (200 g as/ha) extracted straws were subjected to soxhlet extraction using water as solvent. This process resulted in the released of 60 - 74 % of the remaining ^{14}C residue. It was found that up to 54% of the chem3 water extract was base soluble, while HPLC analysis showed that some 27 - 29 % of it consisted of chem3ide. It is not possible, on the basis of the information available, to explain why chem3ide was released only by the water extraction other than to suggest that it had been released by hydrolysis.

Acid and base hydrolysis using 1N HCl, 1N NaOH, and 6 N HCl released 85.6 and 61.4 % of the non extracted ^{14}C from acetonitrile / water extracted straw.

5. Identity of residues in forage

In the case of forage, HPLC analysis of the different extracts indicated that they appeared to contain all of the peaks found in the straw extracts. The difference between the straw and forage extracts were the ratios at which the different peaks were present. In forage, at an application rate of 70 g as/ha, the main peaks present were the parent chemx - 55.4 % of the matrix ^{14}C (chem3 label), 65.7 % of the matrix ^{14}C (chem2 label) - and the desmethyl compound - 6.4 % of the matrix ^{14}C (chem3 label), 4.3 % of the matrix ^{14}C (chem2 label), with all of the other chromatographic fractions (chem1-1 to chem2-7 and chem3-1 to chem3-7) present at concentrations less than 0.05 mg/kg.

6. Development of analytical procedures

Analytical procedures developed in the course of the study indicate that if chemx and its metabolites are subjected to acid hydrolysis, degradation proceeds as follows -

1 N HCl at 95°C for 55 minutes degrades parent chemx and chem3ide containing moieties to the chem3ide molecule - if parent is degraded xxxxxxx (chem2-7) is also released

1 N HCl at 150°C for 70 minutes degrades parent chemx and chem2 containing metabolites to the sulphone metabolite.

This data was used as the basis for the development of the method of analysis which has been submitted for the analysis of residues of chemx in wheat where the "sulfone" target analyte is used to quantify residues present (see Part 2).

Table IIA 6.2.1-4 Metabolites detected in wheat straw following post-emergence treatment with chemx

	Content in mg/kg (% of total ^{14}C present in the extract)			
	Chem2 chemx 70 g as/ha	chem2 chemx 200 g as/ha	chem3 chemx 70 g as/ha	chem3 chemx 200 g as/ha
TRR in matrix.	0.32	1.1	0.31	1.1
Chemx [chem2-9 = chem3-9]	0.13 (41%)	0.5 (45.1)	0.1 (33.4)	0.44 (39.6)
Desmethyl metabolite [chem2-8 = chem3-8]	0.009 (2.9)	0.034 (3.1)	0.013 (4.1)	0.045 (4.1)
Xxxxxxx [chem2-7]	0.01 (3.5)	0.037 (3.4)		
Xxxxxx [chem2-4]	0.022 (6.7)	0.078 (7.1)		
Xxx [chem3-7]			0.018 (5.7)	0.046 (4.2)
Xxxx [chem3-5]			0.011 (3.5)	0.034 (3.1)
Xxyx [chem2-3]	0.003 (1)	0.011 (1)		
Chem2-6	Circa 4.3 - 4.4 % of the ^{14}C present in the extract. Found only in the chem2 labelled straw – found on analysis to consist of many components, none of which were identified. 33 % of this fraction could be hydrolysed to the sulphone, confirming that this fraction contained metabolites with the chem2 moiety.			
Chem2-5	Circa 2.1 – 2.3 % of the ^{14}C present in the extract. Found only in the chem2 labelled straw. A multicomponent fraction which on hydrolysis yielded 53 % of the sulphone molecule.			
Chem2-1/2	Circa 5.0 –5.9 % of the ^{14}C present in the extract. On analysis using ion pair chromatography found to contain many components - on hydrolysis the sulphone molecule was not formed. This fraction does not contain an intact chem2 ring and was found only in the chem 2 labelled straw.			
Chem3-6	Circa 4.4 – 4.8 % of the ^{14}C present in the extract. Found only in the chem3 labelled straw. A multicomponent mixture of which 12.9 % was hydrolysable to chem3ide.			
Chem3-4	Circa 4.7 – 5.2 % of the ^{14}C present in the extract and found only in chem3 labelled straw.			
Chem3-3	Circa 4.8 – 5.2 % of the ^{14}C present in the extract and found only in chem3 labelled straw. This was a multicomponent fraction of which 36 % was hydrolysable to chem3ide.			
Chem3-1/2	Circa 7.5 – 7.9 % of the ^{14}C present in the extract and found in chem3 labelled straw. This did not yield any chem3ide when hydrolysed indicating that the metabolites present contained an already degraded chem3 ring. Chem3-2 was isolated from forage only.			
Chem3ide	Soxhlet extraction with water of chem3 (high rate) [solvent extracted straw] released 73.7 % of the remaining ^{14}C which was found on analysis to contain circa 0.027 mg/kg of chem3ide			
Xxyx [chem2-3]	In the case of the chem2-3 peak, which corresponds to xxyx, it was found it contains circa 15 % of xxyx.			
% of TRR ^{14}C identified.	72.2	77.6	68.9	73.4
% of TRR ^{14}C not extracted from straw with acetonitrile / water .	12.4	10.6	16.9	16.1
Total ^{14}C accounted for	84.6	88.2	85.9	89.5

7. Identification of metabolites

The identity of the various metabolites was investigated by comparison of the extractable residue with 12 different standards that were synthesised and were proposed as possible metabolites. LSC analysis of the extractable residue showed that while there are at least 9 different ^{14}C zones in the HPLC chromatograms, parent chemx is the main residue present. 6 other metabolites were also identified in the wheat straw (Table IIA 6.2.1-4 and Figure IIA 6.2.1-1), of which the desmethyl metabolite (chem2-8 / chem3-8) was the only metabolite common to both labels. The remaining unidentified components of the extracted residue were characterised by hydrolysis to sulphone or chem3ide molecules thus confirming the presence of these moieties in the metabolites under investigation; further analysis of the HPLC fractions (collected using preparative HPLC) using different HPLC conditions to determine if fractions isolated corresponded to one or more component molecules; partitioning the ^{14}C residues between ethyl acetate and water (pH 1 and 7) with a view to determining the polarity of the residue.

It was determined in this way that HPLC fractions chem2-6, chem2-5, chem2-1/2, chem3-6, chem3-3 and chem3-1, which were present at between 2 and 7.9 % of the total ^{14}C residue (Table IIA 6.2.1-4), contained several component fractions. In the case of the chem2-3 fraction, which accounted for 6.5 % of the TRR only 15 % was identified as being xxyx.

Chem3ide was not extracted from straw with acetonitrile / water but was detected when the acetonitrile / water extracted straw was further extracted with water using a soxhlet apparatus. It is possible that chem3ide was extracted at this stage as a result of the hydrolysis of bound metabolites containing chem3ide.

At the time of analysis 12 different reference standards were used with a view to identifying the metabolites isolated. The reference compounds used were -

chemx (chem2-9 / chem3-9)	desmethyl chemx (chem2-8 / chem3-8)
xxxx (chem3-5)	xxx (chem3-7)
chem3ide	chem3ide-N-glucoside
monohydroxychem3ide	xxxxxxx (chem2-7)
yyyyy	xxyyx
xxxxxx (chem2-4)	xxyx (chem2-3).

Procedures used to identify the metabolites present -

- chemx (chem2-9 / chem3-9) and desmethyl chemx (chem2-8 / chem3-8) were fractionated by preparative HPLC, purified using other HPLC systems and identified by LC/FAB/MS and by co-elution on HPLC. MS confirmation was not undertaken for the desmethyl chemx (chem2-8 / chem3-8) fraction,

- xxxxxxx (chem2-7) was fractionated by preparative HPLC and was identified by co-elution with standards on 2 HPLC systems and was confirmed with HPLC/FAB/MS,

- all the identified metabolites were confirmed by co-elution with standards on different HPLC systems,

- those HPLC fractions which were isolated and which did not correspond to the standards used were generally further characterised on a different HPLC system and hydrolysed to determine what % of the ^{14}C was degradable to the sulphone or chem3ide molecules. The hydrolysis data indicated whether the metabolite fraction under consideration still retained intact chem3 or chem2 rings as appropriate.

8. Proposed degradation pathway

A metabolic pathway for chemx is proposed (Figure IIA 6.2.1-1). It is not possible from the data available to propose the identity of metabolites other than those resulting from direct degradation of parent chemx.

Figure IIA 6.2.1-1 Postulated pathways of formation of metabolites identified in straw following post-emergence treatment with chemx

Pathway Omitted

III. CONCLUSIONS

On the basis of the data presented, it is evident that -

- residues in grain (including parent and all metabolites) following application of chemx at 20 g as/ha post- emergence, which is the recommended GAP, should not be detectable at levels greater than 0.01 mg/kg;

- residues in straw at harvest will be greatest following post-emergence application of chemx. The residue consists mainly of parent chemx - 33 to 45 % of the total residue. The total residue in straw (parent compound and all sulphone containing metabolites) following post-emergence application of chemx at 20g as/ha is expected to be present at ≤ 0.1 mg/kg.

- total residues in straw following pre-emergence application of chemx at 20 g as/ha (a use that is not proposed) should be < 0.05 mg/kg of which the parent molecule constitutes *circa* 10 % and the chem2-7 and chem2-4 molecules constitute *circa* 25 % each.

- following application of chemx in accordance with the proposed GAP, residues of chemx may be detected in straw whereas residues of parent compound or of any metabolite, should not be detectable in grain.

The most appropriate residue definition for chemx, when applied to wheat, is parent chemx. However, it is not possible to restrict the residue definition to the parent molecule, since the method of analysis developed to quantify residues will determine residues of parent chemx and those of all residues that can be hydrolysed to the ethylsulphone degradation product. Under the circumstances the residue definition proposed is **"the sum of chemx and its ethylsulphone metabolites, expressed as chemx".**

(Green RG 1994)

IIA 6.2.1.2 Metabolism, distribution and expression of residues in other plant species

Since use on crops other than wheat is not proposed at this time, metabolism studies on other species were not presented. In the event of an extension of use to other crops is sought, further appropriate and relevant metabolism studies will be submitted at that time.

IIA 6.2.1.3 Comparison of plant and animal metabolic pathways

Only 2 of the 6 identified wheat metabolites, the desmethyl metabolite the xxxxxxx (chem2-7), were found in the rat metabolism study. The metabolic pathway in rats appears to differ somewhat from wheat in that in wheat cleavage of the chem2 xxx bond appears to be of greater significance whereas in rats the demethylation and oxidation of the chem3 ring appears to be more important. To obtain a more precise comparison between the metabolic pathways in plants and in those in animals a further animal metabolism study is required in which tissues and organs are analysed with a view to fully characterising the residues present. Since residues in treated wheat used for human and animal consumption are very low and as each of the wheat metabolites not identified in rat excreta are individually present at less than 7 % of the wheat straw residue, it is considered that the toxicological implications arising are minimal. However, an animal metabolism study would provide useful additional information for the purposes of elaborating the residue definition.

IIA 6.2.2 Metabolism, distribution and expression of residues in poultry

The proposed GAP for chemx relates to use on winter and spring wheat only. Since residues in . .....*(in the interest of brevity and to avoid the inference that particular justifications have universal application, the remainder of the text is omitted)*

.
.
.
.
.

IIA 6.2.3 Metabolism, distribution and expression of residues in a lactating ruminant species

Report: IIA 6.2.3/01 - Ladeus VG *et al* 1996, Metabolism of Chemx in Lactating Goats, Chemco Report XX 11713

Guidelines

EPA Pesticide Assessment Guideline 171-4 (b): Subdivision O, Residue Chemistry . The report also meets the requirements of EU Directive 91/414.EEC, Annex II, point 6.2.

GLP: Fully GLP compliant [17].

Executive summary

In a goat metabolism study, chemx (98 % purity) labelled with ^{14}C in the C-2 position of the chem2 ring, or the C-5 position of the Chem3 ring was administered orally using gelatine capsules to individual goats at dose levels of 125 mg daily (equivalent to 50 mg/kg bw) for three days. A single concurrent control was administered gelatine capsules alone.

Unchanged chemx was the major terminal residue identified in liver, kidney, muscle and milk: 13.0 - 89.4 % of the total radioactive residue (TRR) (0.0019 - 0.15 mg/kg). Other metabolites identified in these various tissues and milk, in decreasing order of magnitude were metabolite 2 at 6 – 25 % of the TRR (0.0020 - 0.032 mg/kg), metabolite 1 at 1.1 -10.7 % of the TRR (0.00099 - 0.015 mg/kg) and metabolite 11 at 1.5 - 18.9 % of the TRR (0.0020 - 0.0057 mg/kg).

The overall accountability of the study was good. More than 85 % of the administered dose of chemx was excreted within 3 days of dosing. In both treatment animals, tissues retained only low levels of the administered dose – less than 0.02 % of the TRR (0.31 and 0.37 mg/kg) for the chem2 and chem3 goats respectively. TRR values in individual tissues were as follows: kidney and liver 0.14 and 0.18 mg/kg; muscle 0.0079 and 0.021 mg/kg; fat < 0.0022 and 0.0079 mg/kg; while the TRR values in milk were 0.027 and 0.030 ppm for the chem2 and chem3 goats respectively. 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 (≥ 35% of the TRR) of non-extractable residues present. Residues in fat were not characterised because of their low TRR values - < 0.0022 - 0.013 % (<0.0022 - 0.0079 mg/kg). Overall unextractable residue levels were low and where further characterised were found to contain both the chem2 and the chem3 moieties, indicating that they were mainly present as parent chemx or its chem2 containing metabolites. The low level of bioaccumulation observed was consistent with the log K_{ow} value of < 1 for parent chemx (range of pH 5-9).

On the basis of the data presented and as a consequence of the specificity limitations imposed by the method of analysis available, it is suggested that the residue of concern be defined as "the sum of chemx and its ethyl sulphone metabolites, expressed as chemx"

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: chemx -

	chem2 ring labelled:	^{14}C in the C-2 position (label 13 chemx); specific activity 11.4 mCi/mmol;
	chem3 ring labelled:	^{14}C in the C-5 position (label 14 chemx); specific activity 10.5 mCi/mmol;
Description:	White powder	
Lot/Batch #:	NPD-9307-5386-T	
Purity:	chem2 ring labelled:	radiochemical purity ≥ 98 % [18]
	chem3 ring labelled:	radiochemical purity ≥ 98 % [18]
CAS #:	16335-17-2	
Stability of test compound:	The test material was stable for at least 7 days at room temperature.	

2. Test animals -

Species:	Goat
Gender:	Female
Age:	30 to 42 months at dosing

Weight at dosing:	xx.xxx to xx.xxx kg
Number of animals:	one per treatment and concurrent control
Acclimation period:	minimum of 10 days quarantine, followed by 24 hours acclimation to individual metabolism cages
Diet:	*ad libitum* (type not reported)
Water:	Tap water, *ad libitum*
Housing:	Individual metabolism cages
Husbandry:	Husbandry conditions were in accordance with the USPHS-NIH publication *Guide to the Care and Use of Laboratory Animals*.
Environmental conditions -	
Temperature:	22 ± 2° C
Humidity:	55 ± 10 %
Air changes:	16 - 20 changes/h
Photoperiod:	Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS

1. **Dosing regime –**

Oral:	**Amount of dose:**	50 mg/kg bw/day (label 13 chemx or label 14 chemx)
	Food consumption:	xx kg/day
	Vehicle:	gelatine capsule
	Timing:	once daily
	Duration:	three days

2. **Sample collection:**

Milk collection:	twice daily.
Urine and faeces collection:	once daily.
Interval from last dose to sacrifice:	< 24 hours
Tissues harvested & analysed:	kidney, liver, muscle, fat and GI tract with content.

3. **Storage stability of samples**

Samples of control liver and milk were spiked with chem2- and chem3-labelled chemx and were stored in a freezer at -20ºC for 14-15 days. Following this short storage period, the samples were extracted with acetonitrile and water (1 : 1 by volume) and were analysed using high performance liquid chromatography with a radioactive flow detector (HPLC/RAD). More than 95 % of total radioactivity was accounted for in the extracts. The chromatograms showed only one well defined peak. The retention time of the peak corresponded to that of chemx. Therefore, chemx appears to be stable in frozen liver and milk samples stored for 14-15 days.

All chem2 and chem3 tissue and milk specimens were kept frozen at –20 ºC, from time of sacrifice (July 22, 1994) until analysis (August 16-24, 1995). All analyses were conducted within a 4-6 month time frame, consequently, a storage stability study is not necessary.

II. RESULTS AND DISCUSSION

A. TOTAL RADIOACTIVE RESIDUES (TRRs)

The results indicate that ^{14}C-residues were comparable for both labelling positions (Table IIA 6.2.3-1). The overall ^{14}C recoveries of the administered dose were 86 % (44.60 mg/kg bw) for the chem2 goat and 86 % (39.86 mg/kg bw) for the chem3 goat. The recovered radioactivity was primarily in urine, faeces and gut contents: 85.9 % (44.2 mg/kg bw) (chem2) and 85.7 % (39.5 mg/kg bw) (chem3) of the administered dose. It therefore appears that more than 99.9 % of the recovered radioactivity was excreta-related.

Milk accounted for 0.027 % (0.027 mg/kg bw) and 0.040 % (0.030 mg/kg bw) of the administered dose in the chem2 and chem3 goats, respectively. The residues in fat were not characterised because of the levels involved (< 0.0022-0.013 % of TRR). The low levels found in fat are consistent with the low bioaccumulation potential of chemx.

Residue concentrations in tissues were: 0.14 and 0.18 mg/kg bw in kidney and liver; 0.027 and 0.030 mg/kg bw in milk; 0.0079 and 0.021 mg/kg bw in muscle. Combined the tissues (kidney, liver, muscle and fat) contained 0.011 % (0.370 mg/kg bw) (chem2) and 0.171 % (0.309 mg/kg bw) (chem3) of the administered dose.

On the basis of the data generated it is apparent that if chemx treated wheat forage, containing maximum residues of 3.0 mg/kg was fed to a lactating goat, quantifiable residues of chemx and its metabolites are unlikely to be detectable in milk and tissues at levels greater than 0.01 mg/kg.

Table IIA 6.2.3-1 Total radioactive residues (TRRs) in milk tissues and excreta

Matrix	Chem2		Chem3	
	mg/kg	% of Dose	mg/kg	% of Dose
Kidney	0.18	0.0099	0.14	0.0083
Liver	0.18	0.051	0.14	0.04
Milk	0.027	0.027	0.03	0.04
Muscle	0.0079	0.045	0.021	0.11
Fat	< 0.0022	< 0.0022	0.0079	0.013
Urine	9.5	29	8.5	38
Faeces	28	46	26	40
Upper GI tract	1.1	4	0.92	2.6
Lower GI tract	5.6	6.9	4.1	5.1
Total Recovery	**44.6**	**86**	**39.86**	**86**

B. Extraction and hydrolysis of residues

On the basis of the results of extraction efficiency tests, it was decided to extract the radioactivity in samples of chem2 and chem3 liver, kidney and muscle tissues using three portions of acetonitrile and water (3 : 1 by

volume). For extraction of goat milk, three portions of acetonitrile and water (1 : 1 by volume) was used, since use of acetonitrile and water at a ratio of 3 : 1 resulted in the extraction of too much milk fat. Aliquots of the extracts were analysed using liquid scintillation counting (LSC). The extracted pellet was dried under high vacuum, and triplicate portions were analysed using combustion and LSC.

Extracts of milk, tissue, faecal samples and urine were analysed using quantitative HPLC/LSC. A Beckman Ultraspere Cyano HPLC column and a Beckman Ultraspere ODS C18 column were used to determine whether or not there was a correlation between radioactive peaks and the retention times of co-injected non-radioactive reference compounds – the latter were detected using a UV detector.

The bulk of the identified radioactivity was of compounds containing the chem2 moiety. Acid hydrolysis experiments were conducted on extracts from chem2 kidney, liver, milk and muscle, to determine whether or not chemx hydrolysed to metabolite 7 in the presence of a mild acid (1N HCl). In this case, analysis was achieved by qualitative HPLC/LSC.

C. Characterization and Identification of Residues

Non-extractable residues in chem2 muscle, chem3 muscle and chem3 liver were characterized following sequential extractions. The tissue samples were ground in extraction solvents using a TissueMizer®. The extraction sequence used consisted of two extractions with acetonitrile and water (3 : 1 by volume), followed by a further extraction using 0.1 N HCl and a final extraction using 0.1 N NaOH. The extracts were analysed using the same quantitative HPLC/LSC method as that used for the extractable residues of milk and tissues.

To obtain samples for metabolite identification, radioactive residues in chem3 milk, chem2 kidney and chem3 urine extracts were fractionated and purified by preparative HPLC.

Parent chemx, and metabolite 2 from chem2 kidney extracts were analysed using fast atom bombardment mass spectrometry (FAB/MS) to confirm results obtained using HPLC retention time data.

Metabolite 11 was isolated from urine (richest source) using preparative HPLC fractionation and was identified using negative ion HPLC/ESI/MS. Derivatization techniques and mass spectrometry experiments on derivatives of metabolite 11 from milk and urine showed that metabolite 11 samples from both sources had the same structure.

The distribution of the parent chemx and its metabolites in kidney, liver, milk and muscle is summarized in Table IIA 6.2.3-2.

1. Kidney

Total extractable residues accounted for 98.3 % of the TRR (0.177 mg/kg bw) and 94.9 % of the TRR (0.133 mg/kg) for the chem2 and chem3 kidneys, respectively. Non-extractable residues were low at < 5.1% of the TRR (0.0073 mg/kg) and were not further analysed. Parent chemx was the most abundant residue detected at 74.6 and 89.4 % of the TRR (0.13 mg/kg).

Total identified residues in chem2 and chem3 kidney accounted for > 93 % of the TRR (> 0.13 mg/kg). Three metabolites were identified in quantifiable amounts: metabolite 1 at 1.1 and 2.9 % of the TRR (0.0019 and 0.0039 mg/kg), metabolite 2 at 17.7 % of the TRR (0.0032 mg/kg) in the chem2 treated goat and metabolite 11 at 1.5 % of the TRR (0.0020 mg/kg) in the chem3 treated goat. Two additional

Table IIA 6.2.3-2 Distribution of parent chemx and metabolites in goat kidney, liver, milk and muscle

Metabolite Fraction	Kidney				Liver				Milk				Muscle			
	Chem2 (TRR: 0.18 mg/kg)		Chem3 (TRR: 0.14 mg/kg)		Chem2 (TRR: 0.18 mg/kg)		Chem3 (TRR: 0.14 mg/kg)		Chem2 (TRR: 0.027 mg/kg)		Chem3 (TRR: 0.030 mg/kg)		Chem2 (TRR: 0.0079 mg/kg)		Chem3 (TRR: 0.021 mg/kg)	
	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR
Chemx	0.13	74.6	0.13	89.4	0.15	84.8	0.09	69	0.024	88.8	0.021	68.3	0	23.5	0	13
Metabolite 1	0	1.1	0	2.9	0.0047	2.6	0.02	10.7	ND	ND	0	3.3	ND	ND	ND	ND
Metabolite 2	0.032	17.7	ND	ND	0.011	6	ND	ND	0.0024	8.9	ND	ND	0	25	ND	ND
Metabolite 11 (Chem3-2)	ND	ND	0	1.5	ND	ND	ND	ND	ND	ND	0.01	18.9	ND	ND	ND	ND
Chem2-1	0	1.5	ND	ND	0.001	0.4	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Chem2-2	0	0.9	ND	ND	0.0024	1.3	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Chem3-1	ND	ND	ND	ND	ND	ND	0	0.7	ND	ND	0	2	ND	ND	ND	ND
Chem3-4	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0	11.4
Chem3-6	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0	38
Total Identified	0.1639	93.4	0.136	93.8	0.1657	93.4	0.109	79.7	0.0264	97.7	0.028	90.4	0	48.5	0	13
Total Extractable	0.177	98.3	0.133	94.9	0.174	96.6	0.116	82.9	0.027	99.7	0.029	97.4	0.01	64.6	0.01	65.1
Total Unidentified	0	2.4	ND	ND	0.0032	1.7	0	0.7	ND	N.D.	0	2	N.D.	N.D.	0.01	49.4
Bound	0	1.7	0	5.1	0.0061	3.4	0.02	16.4	0	0.3	0	2.6	0	35.4	0	34.9
Total	0.18	100	0.14	100	0.18	100	0.139	99.3	0.027	100	0.03	100	0.01	100	0.02	100
Accountability	100		100		100		99.3		100		100		100		100	

ND: Not detected Total Unidentified = Total Extractable - Total Identified Bound = TRR - Total Extractable

metabolites present at ≤ 1.5 % of the TRR were characterised as containing the chem2 ring moiety. No metabolite fractions containing the chem3 moiety were detected.

2. Liver

Total extractable residues accounted for 96.6 % of the TRR (0.174 mg/kg bw) and 82.9 % of the TRR (0.116 mg/kg) for the chem2 and chem3, livers respectively. Non-extractable residues represented 3.4 % of the TRR (0.0061 mg/kg) and 16.4 % of the TRR (0.023 mg/kg), respectively for the chem2 and chem3 goats respectively.

Total identified residues in chem2 and chem3 liver accounted for 93.4 % of the TRR (0.166 mg/kg) and 79.7 % of the TRR (0.109 mg/kg), respectively. Parent chemx was the most abundant residue in the extractable fraction of chem2 and chem3 livers representing 69.0 and 84.8 % of the TRR (0.094 and 0.15 mg/kg). Two metabolites were identified in quantifiable amounts: metabolite 1 was detected in both chem2 and chem3 livers at 2.6 and 10.7 % of the TRR (0.0047 and 0.015 mg/kg) while metabolite 2 was detected in the chem2-radiolabelled liver at a low concentration - 6.0 % of TRR (0.011 mg/kg). The residues present in subsequent fractions were not characterised due to their low levels (≤ 1.3 % of TRR).

3. Milk

Total extractable residues accounted for 97.4 and 99.7 % of TRR (0.027 and 0.029 mg/kg) in milk from the chem2 and chem3 goats respectively. Non-extractable residues did not exceed 2.6 % of the TRR (0.0008 mg/kg). It was therefore concluded that additional analyses were not warranted to characterise bound milk residues.

Total identified residues in milk from chem2 and chem3 goats were 90.4 and 97.7 % of the TRR (0.0264 and 0.0277 mg/kg) respectively. Unchanged chemx was the most abundant residue in the extractable fraction of both chem2 milk at 68.3 % of the TRR (0.021 mg/kg) and chem3 milk at 88.8 % of the TRR (0.024 mg/kg). Three metabolites were identified in quantifiable amounts: metabolite 1 was detected in chem3 milk only at 3.3 % of the TRR (0.00099 mg/kg), metabolite 2 was detected in chem2 milk only at 8.9 % of the TRR (0.0024 mg/kg), while metabolite 11 was detected in the chem3-radiolabelled milk sample at a concentration of 18.9 % of the TRR (0.0057 mg/kg).

4. Muscle

Total extractable residues accounted for 64.6 % of the TRR (0.0051 mg/kg) and 65.1 % of the TRR (0.014 mg/kg) in muscle of chem2 and chem3 goats, respectively. Non-extractable residues represented 35.4 % of the TRR (0.0028 mg/kg) and 34.9 % of the TRR (0.0072 mg/kg) in muscle of chem2 and chem3 goats respectively. The non-extractable residues were further fractionated using acetonitrile and water (3 : 1 by volume) and acid and base. Two metabolite fractions were identified in chem3 muscle as a result - chem3-4 at 11.4 % of the TRR (0.0024 mg/kg) and chem3-6 at 38 % of the TRR (0.0078 mg/kg). Due to their very low concentrations, they were not further characterised.

Total identified residues accounted for 48.5 % of the TRR (0.0039 mg/kg) and 13 % of the TRR (0.0027 mg/kg) in chem2 and chem3 goats, respectively. Parent chemx was detected in muscle tissue from the chem2 goat at 13.0 % of the TRR (0.0019 mg/kg) and in muscle tissue from the chem3 goat at levels of

23.5 % of the TRR (0.0027 mg/kg). It was not however the most abundant residue in the extractable fraction. In muscle tissue from the chem2 goat, metabolite 2 was detected at a concentration slightly above that of parent chemx - 25.0 % of the TRR (0.0020 mg/kg). No other metabolite fractions were detected in the muscle tissue from the chem2 goat.

5. Urine and Excreta

Unchanged chemx was the predominant residue in the extracts of urine and faeces. Traces of metabolite 1 and metabolite 2 were also found in urine and faeces from both goats. Traces of metabolite 11 were detected in urine from the chem3 goat urine. These findings are indicative of rapid clearance of chemx and its metabolites and also are indicative of a low propensity to accumulate in milk and tissues.

6. Proposed metabolic pathway

An overall metabolic pathway for chemx is proposed (Figure IIA 6.2.3-1). It is postulated that degradation of chemx occurs *via* hydroxylation of the chem2 ring at the 5-position, demethylation of chemx to form metabolite 1 and cleavage of the sulfonylurea bridge to form metabolite 2.

Figure IIA 6.2.3-1 Postulated pathway for metabolism of chemx in lactating goats

Pathway omitted

Identification of metabolites (key to Figure IIA 6.2.3-1)

Identification Number	Roman Numeral Identification	Common Name / Code	Chemical Name

III CONCLUSIONS

Chemx and its metabolites were rapidly excreted by lactating goats - more than 99.9 % of the recovered radioactivity was excreta-related. Tissues (kidney, liver, muscle and fat) retained only low levels of the administered dose (0.011 – 0.017 %). Residues in individual tissues were as follows: kidney and liver - 0.14

to 0.18 mg/kg; muscle - 0.0079 to 0.021 mg/kg; fat - < 0.0022 to 0.0079 mg/kg. TRR values for milk ranged from 0.027 to 0.030 mg/kg. The low level of bioaccumulation observed was consistent with K_{ow} value of < 1 for parent chemx (range of pH 5-9).

Parent chemx was the major terminal residue identified in tissues and milk accounting for 13.0 to 89.4 % of the TRR (0.0019 to 0.15 mg/kg). Other metabolites identified in these various tissues and milk, in decreasing order of magnitude were metabolite 2 at 0.0020 to 0.032 mg/kg, metabolite 1 at 0.00099 to 0.015 mg/kg and metabolite 11 at 0.0020 to 0.0057 mg/kg. The metabolite pathway postulated for chemx in goats involves degradation of chemx *via* hydroxylation of the chem2 ring at the 5-position, demethylation of chemx to form metabolite 1 and cleavage of the sulfonylurea bridge to form metabolite 2.

The amounts of unextractable residues present were low. When further extracted and characterised they were found to contain both the chem2 and the chem3 moieties, indicating that they were mainly present as parent compound or its chem2 containing metabolites.

On the basis of the data presented it is evident that parent chemx is the major component of the residue in meat, meat by-products and milk, and accordingly is the moiety that should be used for the purposes of defining the residue of concern. However since the majority of the identified radioactivity (chemx, metabolite 1 and metabolite 2) contained the chem2 ring and since the method of residue analysis proposed, determines parent chemx and all metabolites that can be hydrolysed to the target metabolite 7, it is not possible to restrict the residue definition to the parent molecule only. As a consequence of the limitations imposed by the method of analysis available, it is proposed that the residue be defined as **"the sum of chemx and its ethyl sulphone metabolites, expressed as chemx"**.

IIA 6.3.1 **Residues trials (pre-harvest use on major crops)**

IIA 6.3.1.1 **Good Agricultural Practices (GAPs) relevant to the highest residue levels likely to occur**

Since there are only two uses proposed, those uses are the uses likely to result in the highest residue levels in or on treated products, food and feeds. Details of the uses concerned are provided in Table IIA 6.3.1-1.

Table IIA 6.3.1-1 Good Agricultural Practices (GAPs) proposed for chemx and for which supervised trials data (residues) are submitted

Crop	Country	Formulation type (code) and content of active substance (g/kg)	Application				PHI, days
			Method	Rate kg as/ha	Spray conc, kg as/hL	Number	
Winter Wheat (pr)	Australia	WG 800	Foliar up GS 39 (Zadoks)	0.02	0.008-0.01	1	67-71
Winter Wheat (pr)	Belgium	WG 800	Foliar up GS 39 (Zadoks)	0.02	0.008-0.01	1	74
Spring Wheat (pr)	Canada	WG 800	Foliar up GS 39 (Zadoks)	0.02	0.008-0.01	1	74
Winter Wheat (pr)	France	WG 800	Foliar up GS 39 (Zadoks)	0.02	0.008-0.01	1	70-73
Winter Wheat (pr)	Germany	WG 800	Foliar up GS 39 (Zadoks)	0.02	0.008-0.01	1	69-71
Winter Wheat (pr)	Ireland	WG 800	Foliar up GS 39 (Zadoks)	0.02	0.008-0.01	1	74
Winter Wheat (pr)	Holland	WG 800	Foliar up GS 39 (Zadoks)	0.02	0.008-0.01	1	74
Winter Wheat (pr)	UK	WG 800	Foliar up GS 39 (Zadoks)	0.02	0.008-0.01	1	74
Winter Wheat (pr)	USA	WG 800	Foliar up GS 39 (Zadoks)	0.02	0.008-0.01	1	67-74

Notes: 1 Suggested abbreviations for footnotes to the GAP table:

a	aerial application	pr	proposed registration
fg	field and glasshouse use	st	seed treatment
g	glasshouse use only	t	table grapes only
gs	growth stage restriction	w	wine grapes only
Po	post-harvest use		

2 Application rates should be reported using the following units:

field treatment	kg as/ha
grain treatment, post-harvest	g as/t
furrow treatment	g as/m
space fumigation	g as/m^3
spray concentration	kg as/hL

IIA 6.3.1.2 **Residues resulting from supervised trials**

IIA 6.3.1.2.1 **Residues in cereals - winter wheat**

Reports (one of nine): IIA 6.3.1.2/01 Black A 1995, Chemx residues in wheat following post-emergence application of chemx: German field trials 1994, Chemco Report: XX-30361

(two of nine): IIA 6.3.1.2/02 Black A 1995, Chemx residues in wheat following post-emergence application of chemx: English field trials 1994, Chemco Report: XX-30362

(three of nine): IIA 6.3.1.2/03 Black A 1997, Chemx residues in wheat following a post-emergence application of chemx: Belgian field trial 1995, Chemco Report no XX 30509

(four of nine): IIA 6.3.1.2/04 Black A 1997, Chemx residues in wheat following a post-emergence application of chemx: German field trials 1995. Chemco Report no XX 30511

(five of nine): IIA 6.3.1.2/05 Black A 1997, Chemx residues in wheat following a post-emergence application of chemx: French field trials 1995, Chemco Report no XX 30510

(six of nine): IIA 6.3.1.2/06 Black A 1997, Chemx residues in wheat following a post-emergence application of chemx: UK field trial 1995, Chemco Report no XX 30512

(seven of nine): IIA 6.3.1.2/07 Black A 1997, Chemx residues in wheat following a post-emergence application of chemx: French field trials 1996, Chemco Report no XX 30513

(eight of nine): IIA 6.3.1.2/08 Raine U 1997, Magnitude of the residues of chemx in Canadian wheat raw agricultural commodities, Chemco Report no XX 14397

(nine of nine): IIA 6.3.1.2/09 Raine U 1997, Magnitude of the residues of chemx in US wheat raw agricultural commodities, Chemco Report no XX 14397

Guideline

EPA Pesticide Assessment Guideline, Subdivision O, Residue Chemistry. The report also meets the requirements of EU Directive 91/414/EEC, Annex II, point 6.3.

GLP: Fully GLP compliant [17]

Materials and Methods

The first field program was conducted in 1994 at two locations in Germany and at two locations in the UK. Chemx, formulated as Chemx 2222, was applied at the exaggerated rate of 30 g as/ha to wheat when the crop was at growth stage 25 - 30 (Zadoks). A second field program of was conducted in 1995 and in 1996 at one location in Belgium, 5 in Canada, 4 in the Southern of France, 2 in Germany, 1 in the UK and 25 in the USA. Chemx, formulated as chemx, was applied at the maximum recommended rate of 20 g as/ha to wheat at the crop growth stage of 32 - 39 (Zadoks), according to the proposed label directions for use in the case of the European trials and at twice that rate of application in the case of the north American trials. In addition, in the case of the programme of north American trials, pre-emergence and pre-plant incorporation treatments were included.

Table IIA 6.3.1.2-1 Residues in cereals - wheat

GAP is general for all countries : 20 g as/ha with application from GS 13 to GS 39 as a post emergence herbicide							
GLP and trial details	Crop	Country	Application rate g as/ha	Crop growth stage	PHI (days)	Residues found (mg/kg)	Recovery data
Study 93-SOL-01-D, Report number CCC 30361 - Study to GLP. - Study carried out in 1994.	Winter wheat (variety Toronto)	Germany. Wunstorf - Liethe	30 This application rate is 150 % of GAP	GS 25	0 50 90 97 101	Foliage 1.8 Foliage 0.01 Spikelets <0.01 Stem <0.01 Ear <0.01 Stem <0.01 Grain <0.01 Straw <0.01	**Forage:** mean recovery =79.6 %, RSD = 9.3 {n = 8 in 0.02 - 0.05 ppm fortification range} **Straw:** mean recovery = 72 %, RSD = 6 % {n = 4 in 0.01 - 0.05 ppm fortification range} **Grain:** mean recovery = 80 %, RSD =2 3.3 % {n = 4 in 0.01 - 0.05 ppm fortification range} Residue analysed as the Ethylsulphone
Study 93-SOL-01-D, Report number CCC 30361. - Study to GLP. - Study carried out 1994.	Winter Wheat (variety Pepital)	Germany, Hilgenmissen	30 This application rate is 150 % of GAP	GS 25	0 49 78 92 97	Foliage 2.0 Foliage 0.01 Spikelets <0.01 Stem <0.01 Ear <0.01 Stem <0.01 Grain <0.01 Straw <0.01	
Study 93-SOL-01-UK, Report number CCC 30362. - Study to GLP. - Study carried out 1994.	Winter Wheat (variety Beaver)	UK, Pillerton Priors	30	GS 26-30	0 7 56 74 88 123	Foliage 3.1 Foliage 0.1 Foliage <0.01 Spikelet <0.01 Stem <0.01 Ear <0.01 Stem <0.01 Grain <0.01 Straw <0.01	**Forage:** mean recovery = 79.6 % , RSD = 9.3 {n = 8 in 0.02 - 0.05 ppm fortification range} **Straw:** mean recovery = 72%, RSD = 6 % {n = 4 in 0.01 - 0.05 ppm fortification range} **Grain:** mean recovery = 80 %, RSD = 23.3 % {n = 4 in 0.01 - 0.05 ppm fortification range} Residue analysed as the Ethylsulphone
Study 93-SOL-01-UK, Report number MLL 30362. - Study to GLP. - Study carried out 1994.	Winter Wheat (variety Mercia)	UK, Cotsgrove, Notts.	30 This application is 150 % of GAP	GS 25-30	0 7 56 74 88 114	Foliage 1.6 Foliage 0.1 Foliage <0.01 Spikelet <0.01 Stem <0.01 Ear <0.01 Stem <0.01 Grain <0.01 Straw <0.01	

Table IIA 6.3.1.2-1 Residues in cereals - wheat (continued)

GAP is general for all countries : 20 g as/ha with application from GS 13 to GS 39 as a post emergence herbicide

GLP and trial details	Crop	Country	Application rate g as/ha	Crop growth stage	PHI (days)	Residues found (mg/kg)	Recovery data
Study 95-SOL-01-B, Report number CCC 30509. - Study to GLP. - Study carried out in 1995.	Winter wheat (variety Forby)	Belgium,. Franc Waret	20 This application rate is 100 % of GAP.	GS 39	0 24 74	Foliage 0.2 Foliage <0.01 Grain <0.01 Straw <0.01	**Forage:** mean recovery = 89.8 %, RSD = 11 {n = 11 in 0.01 - 0.05 ppm fortification range} **Straw:** mean recovery = 82 % , RSD = 22.8 % {n = 14 in 0.01 - 0.05 ppm fortification range} **Grain:** mean recovery = 87 %, RSD = 17.6 % {n = 15 in 0.01 - 0.05 ppm fortification range} Residue analysed as the Ethylsulphone.
Study 95-SOL-01-D, Report number CCC 30511. - Study to GLP. - Study carried out 1995.	Winter wheat (variety Ritmo)	Germany, Upstedt	20 This application rate is 100 % of GAP.	GS 39	0 27 71	Foliage 0.3 Foliage <0.01 Grain <0.01 Straw 0.07	**Forage:** mean recovery = 89.8 %, RSD = 11 {n =11 in 0.01 - 0.05 ppm fortification range} **Straw:** mean recovery = 82 %, RSD = 22.8 % {n = 14 in 0.01 - 0.05 ppm fortification range} **Grain:** mean recovery = 87 %, RSD = 17.6 % {n = 15 in 0.01 - 0.05 ppm fortification range} Residue analysed as the Ethylsulphone
Study 95-SOL-01-D, Report number CCC 30511. - Study to GLP. - Study carried out 1995.	Winter wheat (variety Ritmo)	Germany, Hondelage	20	GS 39	0 23 69	Foliage 0.4 Foliage <0.01 Grain <0.01 Straw 0.04	**Forage:** mean recovery = 89.8 %, RSD = 11 {n =11 in 0.01 - 0.05 ppm fortification range} **Straw:** mean recovery = 82 %, RSD = 22.8 % {n = 14 in 0.01 - 0.05 ppm fortification range} **Grain:** mean recovery = 87 %, RSD = 17.6 % {n = 15 in 0.01 - 0.05 ppm fortification range} Residue analysed as the Ethylsulphone
Study 95-SOL-01-UK, Report number CCC 30512. - Study to GLP. - Study carried out 1995	Winter wheat (variety Beaver)	UK, Derbyshire	20	GS 39	0 14 74	Foliage 0.3 Foliage 0.01 Grain <0.01 Straw 0.02	**Forage:** mean recovery = 89.8 %, RSD = 11 {n =11 in 0.01 - 0.05 ppm fortification range} **Straw:** mean recovery = 82 %, RSD = 22.8 % {n = 14 in 0.01 - 0.05 ppm fortification range} **Grain:** mean recovery = 87 %, RSD = 17.6 % {n = 15 in 0.01 - 0.05 ppm fortification range} Residue analysed as the Ethylsulphone

Table IIA 6.3.1.2-1 Residues in cereals - wheat (continued)

Data for the Mediterranean region of the EU

GAP is general for all countries : 20 g as/ha with application from GS 13 to GS 39 as a post emergence herbicide

GLP and trial details	Crop	Country	Application rate g as/ha	Crop growth stage	PHI (days)	Residues found (mg/kg)	Recovery data
Study 95-SOL-01-F, Report number CCC 30510. [Trial no. 95HCPMO 01] - Study to GLP. - Study carried out 1995.	Winter wheat (variety Courtot)	France, Saiguede [**South of EU**]	20	GS 39	0 14 70	Foliage 0.3 Foliage 0.03 Grain <0.01 Straw 0.01	**Forage:** mean recovery = 89.8 %, RSD = 11 {n =11 in 0.01 - 0.05 ppm fortification range} **Straw:** mean recovery = 82 %, RSD = 22.8 % {n = 14 in 0.01 - 0.05 ppm fortification range} **Grain:** mean recovery = 87 %, RSD = 17.6 % {n = 15 in 0.01 - 0.05 ppm fortification range} Residue analysed as the Ethylsulphone
Study 95-SOL-01-F, Report number CCC 30510. [Trial no. 95HCPMO 02] - Study to GLP. - Study carried out 1995.	Winter wheat (variety Courtot)	France, Endofielle [**South of EU**]	20	GS 39	0 10 73	Foliage 0.4 Foliage 0.03 Grain <0.01 Straw <0.01	
Study 96-SOL-01-F, Report Number CCC 30513. [Trial no. 96HCPMO P16] - Study to GLP. - Study carried out 1996.	Winter wheat (variety Artaban)	France, Labastide – Saves [**South of EU**]	20	GS 39	78	Grain <0.01 Straw 0.05	**Forage:** mean recovery = 89.8 %, RSD = 11 {n =11 in 0.01 - 0.05 ppm fortification range} **Straw:** mean recovery = 82 %, RSD = 22.8 % {n = 14 in 0.01 - 0.05 ppm fortification range} **Grain:** mean recovery = 87 %, RSD = 17.6 % {n = 15 in 0.01 - 0.05 ppm fortification range} Residue analysed as the Ethylsulphone
Study 96-SOL-01-F, Report number CCC 30513. [Trial no. 96HCPMO P17] - Study to GLP. - Study carried out 1996.	Winter wheat (variety Artaban)	France, Montauban [**South of EU**]	20	GS 39	78	Grain <0.01 Foliage 0.02	**Forage:** mean recovery = 89.8 %, RSD = 11 {n =11 in 0.01 - 0.05 ppm fortification range} **Straw:** mean recovery = 82 %, RSD = 22.8 % {n = 14 in 0.01 - 0.05 ppm fortification range} **Grain:** mean recovery = 87 %, RSD = 17.6 % {n = 15 in 0.01 - 0.05 ppm fortification range} Residue analysed as the Ethylsulphone

Table IIA 6.3.1.2-1 Residues in cereals - wheat (continued)

GAP is general for all countries : 20 g as/ha with application from GS 13 to GS 39 as a post emergence herbicide

GLP and trial details	Crop	Country	Application rate g as/ha	Crop growth stage	PHI (days)	Residues found (mg/kg)	Recovery data
Study Number 95-13-R4-LA, Report Number CCC XX 14397 - Study to GLP - Study carried out in 1995	Spring wheat (variety Katepwa)	Latcombe, Alberta, Canada	40 This application rate is 200 % of GAP	post	0 14 35 80 80	Foliage 1.47 Foliage 0.16 Hay 0.05 Straw 0.03 Grain <0.01	**Forage:** mean recovery = 85.44 %, RSD = 11 {n =10 in 0.01 - 3.0 ppm fortification range} **Hay:** mean recovery=85.6 %, RSD=21.6% {n = 5 in 0.01 - 1.0 ppm fortification range} **Straw:** mean recovery=85.99 %, RSD=12.38% {n = 7 in 0.01 - 0.2 ppm fortification range} **Grain:** mean recovery = 98.12 %, RSD=14.9% {n = 6 in 0.01 - 0.03 ppm fortification range} Residue analysed as the Ethylsulphone
Study Number 95-13-R4-BL Report Number CCC XX 14397 - Study to GLP - Study carried out in 1995	Spring wheat (variety Teal)	Lethbridge, Alberta, Canada	40 This application rate is 200 % of GAP	post	0 10 36 84 84	Foliage 1.68 Foliage 0.10 Hay 0.08 Straw 0.03 Grain <0.01	**Forage:** mean recovery = 85.44 %, RSD = 11 {n =10 in 0.01 - 3.0 ppm fortification range} **Hay:** mean recovery=85.6 %, RSD=21.6% {n = 5 in 0.01 - 1.0 ppm fortification range} **Straw:** mean recovery=85.99 %, RSD=12.38% {n = 7 in 0.01 - 0.2 ppm fortification range} **Grain:** mean recovery = 98.12 %, RSD=14.9% {n = 6 in 0.01 - 0.03 ppm fortification range} Residue analysed as the Ethylsulphone
Study Number 95-13-R4-SA Report Number CCC XX 14397 - Study to GLP - Study carried out in 1995	Spring wheat (variety Makwa)	Saskatoon, Saskatchewan, Canada	40 This application rate is 200 % of GAP	post	0 9 29 72 72	Foliage 1.74 Foliage 0.46 Hay 0.13 Straw <0.01 Grain <0.01	**Forage:** mean recovery = 85.44 %, RSD = 11 {n =10 in 0.01 - 3.0 ppm fortification range} **Hay:** mean recovery=85.6 %, RSD=21.6% {n = 5 in 0.01 - 1.0 ppm fortification range} **Straw:** mean recovery=85.99 %, RSD=12.38% {n = 7 in 0.01 - 0.2 ppm fortification range} **Grain:** mean recovery = 98.12 %, RSD=14.9% {n = 6 in 0.01 - 0.03 ppm fortification range} Residue analysed as the Ethylsulphone

Table IIA 6.3.1.2-1 Residues in cereals - wheat (continued)

GAP is general for all countries : 20 g as/ha with application from GS 13 to GS 39 as a post emergence herbicide

GLP and trial details	Crop	Country	Application rate g as/ha	Crop growth stage	PHI (days)	Residues found (mg/kg)	Recovery data
Study Number 95-13-R4-AN Report Number CCC XX 14397 - Study to GLP - Study carried out in 1995	Spring wheat (variety Makwa)	Aberdeen, Saskatchewan, Canada	40 This application rate is 200 % of GAP	post	0 9 25 73 73	Foliage 2.45 Foliage 0.28 Hay 0.07 Straw 0.01 Grain not detected	**Forage:** mean recovery = 85.44 %, RSD = 11 {n =10 in 0.01 - 3.0 ppm fortification range} **Hay:** mean recovery=85.6 %, RSD=21.6% {n = 5 in 0.01 - 1.0 ppm fortification range} **Straw:** mean recovery=85.99 %, RSD=12.38% {n = 7 in 0.01 - 0.2 ppm fortification range} **Grain:** mean recovery = 98.12 %, RSD=14.9% {n = 6 in 0.01 - 0.03 ppm fortification range} Residue analysed as the Ethylsulphone
Study Number 95-13-R4-MI Report Number CCC XX 14397 - Study to GLP - Study carried out in 1995	Spring wheat (variety Katepwa)	Minto, Manitoba, Canada	40 This application rate is 200 % of GAP	post	0 7 22 58 58	Foliage 2.64 Foliage 0.23 Hay 0.02 Straw <0.01 Grain <0.01	**Forage:** mean recovery = 85.44 %, RSD = 11 {n =10 in 0.01 - 3.0 ppm fortification range} **Hay:** mean recovery=85.6 %, RSD=21.6% {n = 5 in 0.01 - 1.0 ppm fortification range} **Straw:** mean recovery=85.99 %, RSD=12.38% {n = 7 in 0.01 - 0.2 ppm fortification range} **Grain:** mean recovery = 98.12 %, RSD=14.9% {n = 6 in 0.01 - 0.03 ppm fortification range} Residue analysed as the Ethylsulphone
Study Number 95-13-R4-BL Report Number CCC XX 14397 - Study to GLP - Study carried out in 1995	Spring wheat (variety Teal)	Lethbridge, Alberta, Canada	40.79 This application rate is ~200 % of GAP	ppi	51 NA 87 135 135	Foliage <0.01 Foliage <0.01 Hay <0.01 Straw <0.01 Grain <0.01	**Forage:** mean recovery = 85.44 %, RSD = 11 {n =10 in 0.01 - 3.0 ppm spiking range} **Hay**: mean recovery = 85.6 % RSD = 21.6 {n=5 in 0.01-1.0 ppm spiking range) **Straw:** mean recovery=85.99 %, RSD=12.38 {n = 7 in 0.01 - 0.2 ppm spiking range} **Grain:** mean recovery = 98.12 %, RSD=14.9 {n = 6 in 0.01 - 0.03 ppm spiking range} Residue analysed as the Ethylsulphone

Table IIA 6.3.1.2-1 Residues in cereals - wheat (continued)

GAP is general for all countries : 20 g as/ha with application from GS 13 to GS 39 as a post emergence herbicide

GLP and trial details	Crop	Country	Application rate g as/ha	Crop growth stage	PHI (days)	Residues found (mg/kg)	Recovery data
Study Number 95-13-R4-LA Report Number CCC XX 14397 - Study to GLP - Study carried out in 1995	Spring wheat (variety Katepwa)	Lacombe, Alberta, Canada	38.85 This application rate is ~200 % of GAP	ppi	50 64 85 130 130	Foliage <0.01 Foliage <0.01 Hay <0.01 Straw <0.01 Grain <0.01	**Forage:** mean recovery = 85.44 %, RSD = 11 {n =10 in 0.01 - 3.0 ppm spiking range} **Hay**: mean recovery = 85.6 % RSD = 21.6 {n=5 in 0.01-1.0 ppm spiking range) **Straw:** mean recovery=85.99 %, RSD=12.38 {n = 7 in 0.01 - 0.2 ppm spiking range} **Grain:** mean recovery = 98.12 %, RSD=14.9 {n = 6 in 0.01 - 0.03 ppm spiking range} Residue analysed as the Ethylsulphone
Sample Name 94-13-R4-04 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Cardinal)	Arkansas, USA	39.0 This application rate is ~200 % of GAP	post	0 14 45 71 71	Foliage 2.55 Foliage 0.09 Hay 0.012 Straw <0.01 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone
Sample Name 94-13-R4-19 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Quantum 566)	Colorado, USA	39.0 This application rate is ~200 % of GAP	post	0 14 75 101 101	Foliage 3.04 Foliage 0.21 Hay <0.01 Straw <0.01 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone

Table IIA 6.3.1.2-1 Residues in cereals - wheat (continued)

GAP is general for all countries : 20 g as/ha with application from GS 13 to GS 39 as a post emergence herbicide

GLP and trial details	Crop	Country	Application rate g as/ha	Crop growth stage	PHI (days)	Residues found (mg/kg)	Recovery data
Sample Name 94-13-R4-01 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Coker 9835)	Georgia, USA	39.0 This application rate is ~200 % of GAP	post	0 14 49 78 78	Foliage 1.26 Foliage 0.18 Hay 0.036 Straw 0.010 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone
Sample Name 94-13-R4-10 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Cardinal)	Illinois, USA	39.0 This application rate is ~200 % of GAP	post	0 14 59 86 86	Foliage 1.53 Foliage 0.18 Hay <0.01 Straw <0.01 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone
Sample Name 94-13-R4-15 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Karl)	Kansas, USA	39.0 This application rate is ~200 % of GAP	post	0 14 30 52 92 92	Foliage 2.42 Foliage 0.46 Foliage 0.04 Hay 0.04 Straw <0.01 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone

Table IIA 6.3.1.2-1 Residues in cereals - wheat (continued)

GAP is general for all countries : 20 g as/ha with application from GS 13 to GS 39 as a post emergence herbicide

GLP and trial details	Crop	Country	Application rate g as/ha	Crop growth stage	PHI (days)	Residues found (mg/kg)	Recovery data
Sample Name 94-13-R4-17 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Laredo)	Kansas, USA	39.0 This application rate is ~200 % of GAP	post post post post post pre ppi pre ppi pre pre ppi ppi	0 14 84 106 106 178 181 262 265 283 283 286 286	Foliage 1.15 Foliage 0.70 Hay 0.02 Straw <0.01 Grain <0.01 Foliage <0.01 Foliage <0.01 Hay <0.01 Hay <0.01 Straw <0.01 Grain <0.01 Straw <0.01 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone
Sample Name 94-13-R4-06 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Coker 9835)	Mississippi, USA	39.0 This application rate is ~200 % of GAP	post post post post post pre ppi pre ppi pre pre ppi ppi	0 14 47 77 77 132 132 179 17 209 209 209 209	Foliage 1.25 Foliage 0.13 Hay 0.05 Straw 0.02 Grain <0.01 Foliage <0.01 Foliage <0.01 Hay <0.01 Hay <0.01 Straw <0.01 Grain <0.01 Straw <0.01 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone
Sample Name 94-13-R4-09 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Pioneer 2571)	Missouri, USA	39.0 This application rate is ~200 % of GAP	post post post post post pre ppi pre ppi pre pre ppi ppi	0 14 43 60 60 212 212 255 255 272 272 272 272	Foliage 0.81 Foliage 0.025 Hay 0.015 Straw <0.01 Grain <0.01 Foliage <0.01 Foliage <0.01 Hay <0.01 Hay <0.01 Straw <0.01 Grain <0.01 Straw <0.01 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone

Table IIA 6.3.1.2-1 Residues in cereals - wheat (continued)

GAP is general for all countries : 20 g as/ha with application from GS 13 to GS 39 as a post emergence herbicide							
GLP and trial details	Crop	Country	Application rate g as/ha	Crop growth stage	PHI (days)	Residues found (mg/kg)	Recovery data
Sample Name 94-13-R4-07 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Arapahoe)	Nebraska, USA	39.0 This application rate is ~200 % of GAP	post	0 14 58 83 83	Foliage 2.50 Foliage 0.22 Hay 0.015 Straw <0.01 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone
Sample Name 94-13-R4-14 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Arapahoe)	Nebraska, USA	39.0 This application rate is ~200 % of GAP	post	0 14 80 91 91	Foliage 2.85 Foliage 0.25 Hay <0.01 Straw <0.01 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone
Sample Name 94-13-R4-03 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Coker 9803)	North Carolina, USA	39.0 This application rate is ~200 % of GAP	post post post post post pre ppi pre ppi pre ppi pre ppi	0 14 50 89 89 125 125 175 175 214 214 214 214	Foliage 0.81 Foliage 0.025 Hay 0.015 Straw <0.01 Grain <0.01 Foliage <0.01 Foliage <0.01 Hay <0.01 Hay <0.01 Straw <0.01 Straw <0.01 Grain <0.01 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone

Table IIA 6.3.1.2-1 Residues in cereals - wheat (continued)

GAP is general for all countries : 20 g as/ha with application from GS 13 to GS 39 as a post emergence herbicide

GLP and trial details	Crop	Country	Application rate g as/ha	Crop growth stage	PHI (days)	Residues found (mg/kg)	Recovery data
Sample Name 94-13-R4-18 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Longhorn)	Oklahoma, USA	39.0 This application rate is ~ 200% of GAP	post	0 14 44 79 79	Foliage 1.22 Foliage 0.07 Hay 0.03 Straw <0.01 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone
Sample Name 94-13-R4-12 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Mit)	Texas, USA	39.0 This application rate is ~200 % of GAP	post post post post post pre ppi pre ppi pre ppi pre ppi	0 14 51 78 78 115 115 166 166 193 193 193 193	Foliage 1.78 Foliage 0.33 Hay 0.013 Straw <0.01 Grain <0.01 Foliage 0.010 Foliage 0.010 Hay <0.01 Hay 0.014 Straw <0.01 Straw <0.01 Grain <0.01 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone
Sample Name 94-13-R4-13 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Chisholm)	Texas, USA	39.0 This application rate is ~ 200% of GAP	post	0 8 50 70 70	Foliage 1.15 Foliage 0.19 Hay 0.06 Straw 0.03 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone

Table IIA 6.3.1.2-1 Residues in cereals - wheat (continued)

GAP is general for all countries : 20 g as/ha with application from GS 13 to GS 39 as a post emergence herbicide

GLP and trial details	Crop	Country	Application rate g as/ha	Crop growth stage	PHI (days)	Residues found (mg/kg)	Recovery data
Sample Name 94-13-R4-20 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Pioneer 2157)	Texas, USA	39.0 This application rate is ~ 200% of GAP	post	0 14 44 58 58	Foliage 1.52 Foliage 0.09 Hay 0.05 Straw 0.02 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone
Sample Name 94-13-R4-23 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Stephens)	Washington, USA	39.0 This application rate is ~200 % of GAP	post post post post post pre ppi pre ppi pre ppi pre ppi	0 14 78 95 95 207 207 285 285 302 302 302 302	Foliage 1.59 Foliage 0.04 Hay <0.01 Straw 0.03 Grain <0.01 Foliage <0.01 Foliage <0.01 Hay <0.01 Hay <0.01 Straw <0.01 Straw <0.01 Grain <0.01 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone
Sample Name 94-13-R4-24 Report number XX 14397 - Study to GLP - Study carried out in 1994	Winter wheat (variety Hill)	Washington, USA	39.0 This application rate is ~ 200% of GAP	post	0 14 54 105 105	Foliage 1.77 Foliage 0.11 Hay <0.01 Straw <0.01 Grain <0.01	**Forage:** mean recovery = 87.77 %, RSD = 20 {n =35 in 0.01 - 3.0 ppm spiking range} **Straw:** mean recovery=79.24 %, RSD=10.0 {n = 17 in 0.01 - 1.0 ppm spiking range} **Hay**: mean recovery=82.22 % RSD = 11.88 {n=17 in 0.01-1.0 ppm spiking range} **Grain:** mean recovery = 79.42 %, RSD=11.5 {n = 18 in 0.01 - 1.00 ppm spiking range} Residue analysed as the Ethylsulphone

Findings

The residue studies presented in the chemx dossier were carried out in 4 different EU countries, in Canada and in the USA and provide data relevant to conditions in the Northern European region, in the Mediterranean European region, in Canada and in both the northern and southern regions of the USA. The residue trial study reports on both the field and laboratory elements of the trials, were satisfactory and included copies of the trials protocols, amendments to the protocols, copies of the analytical method used, recovery data, copies of sample chromatograms and information with respect to sample history from the field to the completion of analytical work. The proposed GAP is 20 g as/ha applied post-emergence to winter wheat at GS 13 to GS 39 (one application). The following residue studies were presented -

Northern region of Europe - 8 trials, 4 conducted in 1995 in accordance with the proposed GAP and 4 in 1994 at an application rate which was 150 % of GAP rate, but which was applied at GS 25 - 30 as opposed to GS 39

Mediterranean region of Europe - 4 trials, 2 conducted in 1995 and 2 in 1996, in accordance with the proposed GAP.

Canada - 5 trials conducted in 1995 at an application rate which was 200 % of the GAP rate of application.

USA - 17 trials in 1995 at an application rate which was 200 % of the GAP rate of application.

All of the analytical work associated with the studies was performed in the Chemco Research Laboratory, New York. The analytical work was carried out during two different time periods - Autumn / Winter 1994 for the 1994 residue trials and Autumn / Winter 1996 for the 1995 and 1996 residue trials.

In the case of the **Northern European region**, residues in grain were less than 0.01 mg/kg in the four residue trials conducted in 1994 in which chemx was applied at 150 % of GAP rate of application and in which application was made at GS 25 - 30. The results of all 4 residue trials conducted in 1995, which reflected the proposed GAP, confirmed that residues in grain are less than 0.01 mg/kg. In the case of straw, the highest level found was 0.07 mg/kg.

In the case of the **Mediterranean European region**, residues in grain were less than 0.01 mg/kg in both residue trials conducted in 1995 (chemx applied in accordance with the proposed GAP), a finding that was confirmed by means of the results of the two trials conducted in 1996. In the case of straw, the highest level found was 0.05 mg/kg.

In the case of the **Canadian** trials data, residues in grain were less than 0.01 mg/kg in the five residue trials conducted in 1995 in which chemx was applied at 200 % of GAP rate of application. In the case of straw, the highest level found was 0.03 mg/kg.

In the case of the **US** trials data, residues in grain were less than 0.01 mg/kg in all residue conducted in which chemx was applied at 200 % of GAP rate of application. In the case of straw, the highest level found following post-emergence application was 0.03 mg/kg.

All four sets of data are consistent in that all four show that residues will not be detectable in wheat grain when chemx is applied post-emergence to winter or spring wheat in accordance with the proposed GAP.

Conclusions

The residue data clearly indicates that residues in wheat grain should not be detectable at harvest and that residues in straw will be less than 0.1 mg/kg when chemx is applied (one application per season) at 20 g as/ha not later than GS 39.

It should be noted that the method of analysis used in the residue studies determines both parent and all metabolites that are sulphone precursors. Residues detected in samples will therefore overestimate, by between 10 and 20 %, the concentration of parent chemx present in the samples analysed.

(Black A 1995a; Black A 1995b; Black A 1997a; Black A 1997b; Black A 1997c; Black A 1997d; Black A 1997e; Raine U 1996; Raine U 1997)

IIA 6.4 **Livestock feeding studies**

The proposed GAP for chemx involves application of the compound to winter and spring wheat only. Residues in wheat treated in accordance with the proposed GAP, in the case of grain are < 0.01 mg/kg and in the case of straw are < 0.1 mg/kg. Under these circumstances there is no requirement for to generate and supply feeding studies for dairy cows. Nevertheless, a feedings study was conducted and is reported

IIA 6.4.1 **Livestock feeding study in poultry**

The proposed GAP for chemx relates to use on winter and spring wheat only. Since residues in . .....*(in the interest of brevity and to avoid the inference that particular justifications have universal application, the remainder of the text is omitted)*

.
.
.
.
.

IIA 6.4.2 **Livestock feeding study in lactating ruminant (goat or cow)**

Report: IIA 6.4.2/021 Finnigan D, 1996, Chemx residues in lactating dairy cattle, Chemco Report No: XX 11865

Guidelines

EPA Pesticide Assessment Guideline 171-4 (c): Subdivision O, Residue Chemistry . The report also meets the requirements of EU Directive 91/414.EEC, Annex II, point 6.4.

GLP: Fully GLP compliant [17].

Executive summary

In a dairy cattle feeding study, chemx was administered orally to groups of 3 Holstein cattle by gelatin capsule (with one control group of 3 fed capsules only) for 28 days. The dosages were equivalent to 8.1, 23.5 and 81.7 mg/kg feed.

Residues of chemx in the total diet resulting from wheat treated according to the proposed GAP are expected to be less than 0.1mg/kg feed.

At a feeding level of 8.1 mg/kg feed for 28 days, residues of chemx and chem2 containing metabolites (determined as chemx equivalents) were less than the LOQ (0.004 mg/kg) in raw milk, skim milk fat and muscle. Residues of 0.005 mg/kg (average 0.004 mg/kg), 0.12 mg/kg (average 0.096 mg/kg) and 0.10 mg/kg (average 0.076 mg/kg) were detected in cream, kidney and liver, respectively. At the feeding level of 81.7 mg/kg feed, average residues of chemx and chem2 containing metabolites (expressed as chemx) were less than 0.1 mg/kg in all samples except kidney (0.728 mg/kg) and liver (0.519 mg/kg), a finding indicative of concentration of residues in these organs.

Residues reached a plateau in milk after four days and did not appear to concentrate in the cream fraction. This observation is further supported by the fact that the log K_{ow} for chemx is < 1 at pH 5 - 9.

Since the feeding study was carried out at exaggerated feeding rates (lowest dose 8.1 mg/kg), 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).

I. MATERIALS AND METHODS

A. MATERIALS

1. **Test Material:** chemx
   - **Description:** White powder
   - **Lot/Batch #:** NPD-9503-6466-T
   - **Purity:** 98.5 % [18]
   - **CAS #:** 16335-17-2
   - **Stability of test compound:** The test material was stable for at least 7 days at room temperature.

2. **Test animals -**
   - **Species:** Bovine
   - **Breed**: Holstein
   - **Gender:** Female
   - **Age:** 30 to 42 months at dosing
   - **Weight at dosing:** xxx.xx to xxx.xx kg
   - **Number of animals:** three per treatment and concurrent control group
   - **Acclimation period:** minimum of 28 days quarantine, followed by 24 hours acclimation to individual cubicles
   - **Diet:** *ad libitum* (type not reported)
   - **Water:** Tap water, *ad libitum*
   - **Housing:** Individual cubicles
   - **Husbandry:** Husbandry conditions were in accordance with the USPHS-NIH publication *Guide to the Care and Use of Laboratory Animals*.
   - **Environmental conditions -**
     - **Temperature:** 22 ± 2° C

Humidity: 55 ± 10 %
Air changes: 16 - 20 changes/h
Photoperiod: Alternating 12-hour light and dark cycles

B. STUDY DESIGN AND METHODS

1. **Dosing regime –**

Oral: **Amount of dose:**
Group 1 8.1 mg/kg feed (after AM milking)
Group 2 23.5 mg/kg feed (after AM milking)
Group 3 81.7 mg/kg feed (after AM milking)
Group 4 control group (after AM milking)

Food consumption: xx kg/day
Vehicle: gelatine capsule
Timing: once daily
Duration: 28 days

2. **Sample collection -**

Milk collection: morning and afternoon – pooled on a daily basis for 28 days
Interval from last dose to sacrifice: 18 hours
Tissues harvested & analysed: liver (from distal portion of each lobe), kidney, muscle (shoulder, thigh and loin) and fat (stomach, kidney and skin)

3. **Storage of samples -** at: - 10 °C (14 °F) for a maximum of 159 days. Freezer storage stability data demonstrated that residues of chemx are stable in meat and milk at – 12 °C for up to 169 days.

4. **Extraction and characterization -**

Analytical method & type: RES-095-96, v.0

The method involved extraction of the residue with acetonitrile / water (3 : 1 by volume). Solids were removed by centrifugation and the supernatant was acidified with HCl. The extract was heated to remove the acetonitrile and refluxed to convert the chemx and chem2 containing metabolites present to metabolite 7 residues. The residue was determined using HPLC with fluorescence detection. The LOQ of this method in meat and milk was 0.004 ppm, the LOD was 0.001 ppm. Results are reported as chemx equivalents. Concurrent recoveries obtained from control samples spiked with parent chemx served to validate the method (IIA 6.4.2-1).

Table IIA 6.4.2-1 Method validation

Matrix	Spiking level (ppm)	% Recovery	Standard Deviation
Milk	0.003 – 2.0	96 %	
Cream	0.005 – 2.0	88 %	
Fat	0.005 – 2.0	110 %	
Muscle	0.005 – 2.0	91 %	
Kidney	0.005 – 2.0	88 %	
Liver	0.005 – 2.0	93 %	

II. RESULTS AND DISCUSSION

On the basis of the data generated in supervised field trials (point IIA 6.3.1) it is apparent that residues ranged from <0.008 mg/kg in grain at harvest to 3.0 mg/kg in forage following a 0 day PHI. Residues in processed fractions were not determined. Wheat grain can account for 40 and 50 % of the diet of dairy cattle and beef cattle, respectively. Wheat forage and hay are also fed to beef and dairy cattle (25 and 60%, respectively). Wheat straw (10 % for both beef and dairy), aspirated grain fractions (20 % for both beef and dairy) and wheat milled by-products (40 % in beef cattle and 50% in dairy cattle) can also be used as feed items. The feeding levels used in this study were much greater than the expected maximum residues in commodities fed to beef and dairy cattle (Tables IIA 6.4.2-2 and IIA 6.4.2-3).

At a feeding level of 8.1 mg/kg feed for 28 days, residues of chemx and chem2 containing metabolites (determined as chemx equivalents) were less than the LOQ (0.004 mg/kg) in raw milk, skim milk fat and muscle (Table IIA 6.4.2-4). Residues of 0.005 mg/kg (average 0.004 mg/kg), 0.12 mg/kg (average 0.096 mg/kg) and 0.10 mg/kg (average 0.076 mg/kg) were detected in cream, kidney and liver, respectively. At the feeding level of 81.7 mg/kg, average residues of chemx and chem2 containing metabolites (expressed as chemx) were less than 0.1 mg/kg in all samples except for kidney (0.728 mg/kg) and liver (0.519 mg/kg), a finding indicative of concentration of residues in these organs.

Residues reached a plateau in milk after four days and did not appear to concentrate in the cream fraction. This observation is further supported by the fact that the log K_{ow} for chemx is < 1 at pH 5 - 9.

Table IIA 6.4.2-2 Anticipated dietary burden calculation for dairy cattle

RAC	**% of Total Diet**	**% DM**	**Residues / Proposed MRLs** (mg/kg)	**Residue Intake** (mg/kg)
Anticipated dietary burden (mg/kg)				

Table IIA 6.4.2-3 Anticipated dietary burden calculation for beef cattle

RAC	**% of Total Diet**	**% DM**	**Residues / Proposed MRLs** (mg/kg)	**Residue Intake** (mg/kg)
Anticipated dietary burden (mg/kg)				

Table IIA 6.4.2-4 Residues of chemx and chem2 containing metabolites (expressed as chemx equivalents) in tissues and milk from lactating cows dosed with chemx for 28 days.

Dose (mg/kg feed / equivalents	Residues expressed as equivalents of chemx (mg/kg feed); values in ( ) represent the highest single day value						
	Raw Milk*	Skim Milk**	Cream**	Fat	Muscle	Kidney	Liver
Control	<0.004 [3]	<0.004 [3]	<0.004 [3]	<0.004 [3]	<0.004 [3]	<0.004 [3]	<0.004 [3]
8.1	<0.004 [3] Av <0.004 (<0.004)	<0.004 [3] Av <0.004 (<0.004)	<0.004 0.004 0.005 Av 0.004 (0.005)	<0.004 [3] Av <0.004 (<0.004)	<0.004 [3] Av <0.004 (<0.004)	0.084 0.089 0.115 Av 0.096 (0.12)	0.095 0.064 0.069 Av 0.076 (0.10)
23.5	0.008 0.009 0.008 Av 0.008 (0.019)	0.006 0.008 0.009 Av 0.008 (0.009)	<0.004 0.004 0.006 Av 0.004 (0.006)	<0.004 [2] 0.007 Av 0.004 (0.007)	0.005 0.006 0.005 Av 0.006 (0.006)	0.199 0.223 0.163 Av 0.195 (0.22)	0.136 0.276 0.257 Av 0.223 (0.28)
81.7	0.0154 0.0242 0.0228 Av 0.021 (0.034)	0.0132 0.0239 0.0208 Av 0.0193 (0.024)	0.006 0.012 0.009 Av 0.009 (0.012)	0.044 0.005 0.070 Av 0.040 (0.07)	0.018 0.017 0.024 Av 0.020 (0.024)	0.766 0.412 1.006 Av 0.728 (1.0)	0.522 0.478 0.556 Av 0.519 (0.56) spiked

spiked* Average of 27 days ** Taken from day 14 samples [ ] Number of independent values

III CONCLUSIONS

It is not expected that, consumption of feed commodities treated with chemx in accordance with the proposed label recommendation, will result in detectable residues in milk or tissues (muscle, fat, liver, kidney) of lactating dairy cattle (< 0.004 mg/kg).

(Finnigan D)

IIA 6.5 Effects of industrial processing and/or household preparation

The proposed GAP for chemx relates to use on winter and spring wheat only. Since residues in . .....*(in the interest of brevity and to avoid the inference that particular justifications have universal application, the remainder of the text is omitted)*

.
.
.
.
.

IIA 6.6 Residues in succeeding crops

IIA 6.6.1 Theoretical consideration of the nature and level of the residue

The results of the field soil dissipation studies (Lyons T 1996; Lyons T 1997a; Lyons T 1997b; Lyons T 1997c; Lyons T 1997d; Lyons T 1997e), indicated that three months after treatment (the earliest time of sowing or planting a rotational crop), residue levels in soil are very low (< 0.002 mg/kg). On the basis of the results of the supervised residues trials (Black A 1995a; Black A 1995b; Black A 1997a; Black A 1997b; Black A 1997c; Raine U 1996; Raine U 1997), it is clear that residues in straw are less than 0.1 mg/kg. It therefore is submitted that it is not necessary to conduct and report succeeding crop metabolism and distribution studies.

A confined rotational crop study was however conducted to determine residues in crops grown in soil previously treated with chemx, either in the normal rotation or as a result of the failure of a winter wheat crop following treatment.

IIA 6.6.2 Metabolism and distribution studies on representative crops

Report: IIA 6.6.2/01 Erwell V 1996, Confined rotational crop study with chemx, Report No.: CC-14130

Guidelines

US EPA FIFRA Assessment Guidelines, Subdivision N § 165-184-2

GLP: Fully GLP compliant [17]

Executive Summary

In a crop rotational study, aqueous acetonitrile solutions of radiolabelled chemx (chem2 ring labelled chemx, labelled with ^{14}C at the C-3 position, 100% radiochemical purity and chem3 ring labelled chemx, labelled with ^{14}C at the C-5 position, 99.0 % radiochemical purity) were applied directly to soil (loamy sand) at an application rate of 40 g as/ha (twice the recommended application rate). Lettuce, radish, rye and barley 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. All crops were grown in boxes which were maintained in screen-houses equipped with ventilation fans and windows.

In soil the main degradation products of chemx were chem2 -7 and Chem3ide metabolites in roughly equal proportions. In crops the total radiolabelled residue consisting of chemx, its chem2-7 and chem3ide metabolite were < 0.1 mg/kg. The highest levels were found in cereal straw and hay 60 days after treatment. At the 120 and 361 day sampling intervals there was a higher proportion of chem2 labelled residues than might have been expected on the basis of the levels in soil. This is thought to be a result of differential uptake of soil metabolites by the test crops.

The results of the rotational study are broadly consistent with the results of the soil metabolism study (point IIA 7.1.1) which identified desmethyl chemx as the principle metabolites with metabolite 2 of chem2 labelled chemx accounting for 15 % of the total radioactive residue after 225 days

It is unlikely, that significant residues (> 0.02 mg/kg) will occur in succeeding crops following use of chemx as proposed (20 g as/ha).

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: chemx -

chem2 ring labelled: ^{14}C in the C-3 position; specific activity 28.63 mCi/mmol (applications made on 28 April 1994) and 29.6 mCi/mmol (applications made on 28 April 1995)

chem3 ring labelled: ^{14}C in the C-5 position; specific activity 30.2 mCi/mmol (applications made on 28 April 1994) and 27.56 mCi/mmol (applications made on 28 April 1995)

Description: White powder

Lot/Batch #: CR-2089-R; CR-2084-R; CR-1967-R; CR-1987-R

Purity:
chem2 ring labelled radiochemical purity *circa* 100 % (both applications) [18]

chem3 ring labelled radiochemical purity *circa* 99.6 % (applications made on 28 April 1994); 99.0 % (application made on 28 April 1995) [18]

CAS #: 16335-17-2

Stability of test compound: The test material was stable for at least 7 days at room temperature.

2. Soil: An elder loamy sandy was used.

Table IIA 6.6.2-1 Soil Physicochemical Properties

Soil Series	Soil Type	pH	OM %	Sand %	Silt %	Clay %	Moisture holding capacity (at 1/3 bar)	CEC meg / 100g
Elder	Loamy Sand	*6.4	**1.6	64	20	16	16.34	15.9

* measured in a 1 : 2.5 soil : water suspension ** Organic matter calculated as 1.72 x percent organic carbon

B. STUDY DESIGN

The study was conducted during the period April 1994 to March 1996 by the Chemco Research Laboratory, New York.

1. Experimental conditions

Lettuce, radish and barley were used - crops considered to be representative of leafy, root, and cereal crops, respectively. Rye was also planted because of the possibility that chemx might be phytotoxic to barley during its early growth stages. Rotational crops were grown in boxes (76 cm x 91 cm by 30 cm or 45 cm depth) filled with a sandy loam soil. The boxes were maintained outdoors after application of the test substance. After sowing and during crop development, the boxes were maintained in screen-houses equipped with ventilation fans and windows.

Aqueous acetonitrile solutions of chem2 labelled chemx and of chem3 labelled chemx were applied in late April 1994 onto bare soil at an application rate of 40 g as/ha (twice the recommended field use rate). Due to the phytotoxicity of chemx to barley, no barely samples were obtained from the first experiment. A second experiment was conducted with barley in which application to soil was made in late April 1995.

Crops were sown 30, 120, and 361 days after treatment (DAT). Re-sowings were also carried out at 60 and 89 DAT in the case of barley. The 30 and 60 DAT rotational crops were designed to simulate an emergency re-sowing such as might occur following the failure of the primary crop. The 89, 120, and 361 DAT crops were designed to simulate normal rotations following harvest of the primary crop.

2. Sampling

Lettuce and radish crop samples (roots and tops) were obtained from sowing intervals of 30, 120, and 361 DAT. Barley crop samples (foliage, hay, straw, and grain) were obtained from sowing intervals of 120 and 361 DAT, but not from the sowing interval of 30 DAT, because of phytotoxicity. However, re-sowing after 60 days (straw and grain) and after 89 days (foliage, hay, straw, and grain) provided the necessary raw agricultural commodities (crop matrices) from earlier intervals. Rye crops (foliage, straw, and grain) were obtained following sowings 30 and 120 DAT. A 361 DAT rye planting was not carried out because barley was obtained from that interval. Because all four barley crop matrices were obtained from three planting intervals, it was considered to be the main cereal crop for the study.

II. RESULTS AND DISCUSSION

Analysis of the treated soil at different DAT (Table IIA 6.6.2-2), shows that the main constituents present in the soil extracts are parent chemx and its xxxxxx (chem2-7) and chem3ide metabolites. Details of the total radioactive residues (TRRs) found to be present in rotational crop samples are summarized in Table IIA 6.6.2-3. Residue levels were higher for chem2 labelled chemx than for the chem3 labelled material, the difference being more apparent in the case of 120 and 361 DAT samples. The analytical data for soil (Table IIA 6.6.2-2) indicated that soil degradation of chemx results mainly in the generation of the xxxxxxx (chem2-7) and chem3ide metabolites so differential uptake of residues in the rotational crops must derive from a differential ability on the part of plants to take up these metabolites.

The analytical profiles of lettuce, radish , barley and rye clearly show that –

- the xxxxxxx (chem2-7) metabolite remains a major component of the residue in the rotational crops
- provides evidence to support that conclusion that the other main metabolites found in the chem2 treated crops (chem2-1, chem2-2 and chem2-3) all derive from the xxxxxxx (chem2-7) metabolite.

It was not possible to identify these metabolites but when hydrolysed, chromatograms generated contained a major peak which corresponded to the sulphone derivative.

In the case of the chem3 labelled samples, none of the metabolites formed were identified other than to note that they became progressively more polar with increasing number of DAT.

Analysis of the residues present in the rotational crops using the sulphone as the target analyte (Table IIA 6.6.2-4), showed that 47 - 75 % of the residue will be quantified as chemx in accordance with the proposed residue definition.

Table IIA 6.6.2-2 Composition of soil residues following treatment with chem2 and chem3 labelled chemx

Analyte	Days after treatment	% of total residue present in soil chem2 (chem3) labelled chemx	% extractability of residues from soil for chem2 (chem3) labelled chemx	Remarks
xxxxxxxx (chem2-7)	0 days after treatment	4.1	129 (147.5)	Not present for chem3 label
Chemx		120.9 (126.3)		
chem3ide		(1.6)		Not present in chem2 label
xxxxxxxx (chem2-7)	30 days after treatment	26.9	85.8 (99)	Not present for chem3 label
Chemx		36.2 (39.8)		
chem3ide		(35)		Not present for chem2 label
xxxxxxxx (chem2-7)	120 days after treatment	75.5	123.4 (137.2)	Not present for chem3 label
Chemx		17.2 (15.5)		
chem3ide		(94.8)		Not present for chem2 label
xxxxxxxx (chem2-7)	361 days after treatment	72.1	111.6 (93.5)	Not present for chem3 label
Chemx		17.7 (9.6)		
chem3ide		(66.6)		Not present for chem2 label

Table IIA 6.6.2-3 Total radioactive residues (TRRs) in rotational crops following their cultivation in soil treated with chemx

Crop	Crop portion	TRR (mg/kg) in crops sown (--) days after treatment with chem2 labelled chemx	TRR (mg/kg) in crops sown (--) days after treatment with chem3 labelled chemx
Lettuce	lettuce	0.0011(30d) ; 0.0037 (120d) ; 0.0062 (361d)	0.00046 (60d) ; 0.00067 (120d) ; 0.00086 (361d)
Radish	root	0.0011(30d) ; 0.0029 (120d) ; 0.002 (361d)	0.0009 (60d) ; 0.00053 (120d) ; 0.00094 (361d)
	top.	0.0038 (30) ; 0.016 (120) ; 0.0092(361d)	0.0027 (60d) ; 0.0011 (120d) ; 0.0013 (361d)
Barley	grain	0.0032(60d) ; 0.0016(89d) ; 0.0045(120d) ; .0032(361d)	0.0018(60d); 0.002(89d) ; 0.0018(120d) ; 0.0046(361d)
	forage	0.0059(89d) ; 0.012(120d) ; 0.013 (361d)	0.0023(89d); 0.0091(120d) ; 0.0036(361d)
	hay	0.011 (89d) ; 0.041 (120d) ; 0.032 (361d)	0.0063(89d) ; 0.004 (120d) ; 0.014 (361d)
	straw.	0.087 (60d) ; 0.052 (89d) ; 0.057 (120d) ; 0.074 (361d)	0.013(60d) ; 0.017 (89d) ; 0.0078(120d) ; 0.025 (361d)
Rye.	grain	0.0039 (30d) ; 0.0011 (120d).	No grain data.
	forage	0.0084 (30d) ; 0.01 (120d).	0.0019(30d) ; 0.0012(120d).
	straw	0.011 (30d) ; 0.027 (120d).	No data due to contamination.

When crops were sown on soil which was treated with chemx at a rate of application of 40 g/ha of chemx (twice the proposed GAP rate of application), residues were detected in these crops. The level of TRR residues present were less than 0.01 mg/kg in the case of lettuce, less than 0.005 mg/kg in the case of radish roots and less than 0.02 mg/kg in the case of radish tops, less than 0.005 mg/kg in the case of barley and rye grain and less than 0.1 mg/kg in the case of barley and rye straw, forage and hay.

In all cases, other than radish roots following a period of 30 DAT, parent chemx accounted for less than 5 % of the TRR present. If the TRR is hydrolysed to the sulphone, some 48 to 75 % of the residue degrades to this degradation product (corresponding to the proposed residue definition) (Table IIA 6.6-4).

In the case of crops treated with chem2 labelled chemx, the residue taken up most readily from the soil appears to be the xxxxxxx (chem2-7) metabolite. The further degradation of this metabolite, following its uptake by plants seems to be the main source of the other metabolites found to be present.

Table IIA 6.6.2-4 Comparison of the % sulphone formation in chem2 extracts and metabolite distribution (chem2-1 to chem2-5)

Crop/ Sample	Planting interval [DAT]	TRRs (mg/kg) present in samples analysed	Metabolites chem2-1 to chem2-5 as a % of TRR in the sample [% of parent chemx (chem2-5) present in the sample]	% of total chem2 residue which is converted to the sulphone target analyte.
Barley forage	89	0.0059	35.2 [0.8%]	46.7
	120	0.012	61.8 [not detected]	69.2
	361	0.013	57.3 [not detected]	63
Barley hay	120	0.041	42.7 [not detected]	52.7
	361	0.032	36.6 [not detected]	51
Barley straw	60	0.087	27.2 [0.7%]	65.7
	89	0.052	36.2 [0.6%]	64.4
	120	0.057	34.6 [not detected]	53.5
	361	0.074	30.7 [not detected]	64.5
Rye forage	30	0.0084	76.1 [not detected]	64.4
	120	0.01	62.7 [not detected]	75.2
Rye straw	30	0.011	31.6 [3.8%]	64
	120	0.027	38.2 [not detected]	57.8
Radish roots	30	0.0011	56.4 [18.5, not detected at other dates]	65.9
Radish tops	30	0.0038	70.8 [3.3%]	52.1
	120	0.016	74.2 [not detected]	59.6
	361	0.0092	77.8 [not detected]	63.4
Lettuce	30	0.0011	83 [not detected]	53.8
	361	0.0062	53.9 [not detected]	70.7
In the case of cereal grain the total residues present were always less than 0.005 mg/kg.				

III. CONCLUSIONS

It is considered unlikely, that residue levels greater than the proposed LOQ of 0.02 mg/kg will occur in succeeding crops following use of chemx as proposed (20 g as/ha). Consideration is being given to undertaking further work to determine whether or not residues greater than 0.02 mg/kg could occur in succeeding crops where such crops follow a succession of treated winter wheat crops each of which had been treated with an application of 20 g as/ha per annum of chemx.

(Erwell V 1996)

IIA 6.7 Proposed residue definition and maximum residue levels (MRLs)

IIA 6.7.1 Proposed residue definition

Proposed residue definition (wheat)

On the basis of the data presented relating to metabolism of chemx in plants (point IIA 6.2.1) it is evident that parent chemx is the major component of the residue in wheat grain following post-emergence application of the compound and accordingly it is the moiety which in logic should be used for the purposes of defining the residue. However since the method of residue analysis proposed, determines parent chemx and all metabolites which can be hydrolysed to the target sulphone analyte, it is not possible to restrict the residue definition to the parent molecule only. As a consequence of the specificity limitations imposed by the method of analysis available, it is proposed that the residue be defined as **"the sum of chemx and its ethylsulphone metabolites, expressed as chemx"**.

Proposed residue definition (food of animal origin)

On the basis of the data presented relating to metabolism of chemx in animals (point IIA 6.2.2), it is evident that parent chemx is the major component of the residue in meat, meat by-products and milk, and accordingly is the moiety that should be used for the purposes of defining the residue of concern. However since the majority of the identified radioactivity (chemx, metabolite 1 and metabolite 2) contained the chem2 ring and since the method of residue analysis proposed, determines parent chemx and all metabolites that can be hydrolysed to the target metabolite 7, it is not possible to restrict the residue definition to the parent molecule only. As a consequence of the limitations imposed by the method of analysis available, it is proposed that the residue be defined as **"the sum of chemx and its ethyl sulphone metabolites, expressed as chemx"**.

Should an alternative method of analysis be validated for the determination of parent chemx only, in plant, animal tissues and milk, it would be possible to propose that the definition be restricted to the parent compound only. Consideration is being given to undertaking further work necessary to develop such a method of analysis.

IIA 6.7.2 Proposed maximum residue levels (MRLs)

On the basis of the residues data was generated in Belgium Canada, France, Germany, UK and the USA and reported (point IIA 6.3.1.2), it is evident that residues in wheat grain will not exceed 0.01 mg/kg and that residues in succeeding crops will not exceed 0.01 mg/kg. The limit of quantification for the available method of analysis is 0.02 mg/kg. Accordingly it is **proposed that the MRL for wheat grain be set at 0.02* mg/kg.**

The MRL proposed for all other commodities of plant origin is 0.02* mg/kg.

* denotes at or about the limit of quantification.

IIA 6.7.3 Differences, if any, in the data base submitted in comparison to that provided to the JMPR

Chemx has not been scheduled for evaluation by the Joint Meeting on Pesticide Residues (JMPR). Consequently, data or information has not yet been provided to that organization.

IIA 6.8 Proposed pre-harvest intervals, re-entry intervals or withholding periods to minimize residues in crops, plants plant products, treated areas or spaces and a justification for each proposal

IIA 6.8.1 Pre-harvest intervals (in days) for each relevant crop

The only use proposed is a post-emergence treatment (20 g as/ha) in a single application to winter and spring wheat at growth stage 39 (flag leaf ligule just visible), or earlier. The residues data submitted reflect that time of application. Since only one application is proposed and since that application would at the latest be applied at growth stage 39, involving a minimum pre-harvest interval of 67 days before harvest, the pre-harvest interval should be established at 67 days but, in order that differing growing conditions can be accommodated, it should be expressed in terms of the **latest growth stage for application (growth stage 39)**.

IIA 6.9 Estimation of the potential and actual exposure through diet and other means

IIA 6.9.1 TMDI calculations

IIA 6.9.1.1 Estimates of the potential exposure through diet for Europe (TMDI)

As estimate of potential intake, direct (food made from chemx treated wheat) and indirect (meat, milk, eggs from animals fed with chemx treated wheat) based upon the WHO European region diet is provided (Table IIA 6.9.1-1). Since potential exposure is no more than 0.1 % of the proposed ADI (0.24 mg/kg bw/day), estimates of actual exposure were not prepared.

Table IIA 6.9.1-1 Estimate of the TMDI for chemx (WHO European regional diet)

Commodity.	European intake (g/person /day)	Proposed MRL mg/kg.	Exposure TMDI (mg/kg bw/ day)
Barley	19.8		
Maize flour.	8.8		
Oats.	2.0		
Rye flour.	1.5		
Wheat (total)	178	0.02	0.00006
Rice (total)	12		
Potatoes.	241		
Pulses (total)	9.3		
Sugar (total)	105		
Tree nuts (total)	4.0		
Oilseed rape oil	7.3		
Sunflower oil	8.5		
Pome fruit.	51.3		
Stone fruit.	23		
Grapes	16.1		
Bananas	22.8		
Other fruit.	96		
Endive			
Other vegetables.	298		
Butter.	14	(0.02)**	0.000005
Cheese	28	(0.02)**	0.000009
Milk bovine.	252.5	(0.02)**	0.00008
Meat, bovine.	63.4	(0.02)**	0.00002
Meat , ovine.	10.3	(0.02)**	0.000003
Meat , porcine.	75.8	(0.02)**	0.00003
Poultry, meat.	53.1	(0.02)**	0.00002
Eggs.	37.5	(0.02)**	0.00001
Offal (liver, kidney)	12.3	(0.02)**	0.000004
Total exposure.			0.000241
Proposed ADI.			0.24 mg/kg bw/day
Total dietary exposure (%) of ADI.			0.1 %

In the case of food of plant origin, intakes for wheat only are used in the TMDI estimates as there are no other uses proposed for chemx.

** For the purposes of estimating indirect intake (meat, milk, eggs from animals fed with chemx treated wheat), an MRL of 0.02 mg/kg is assumed (actual residues in grain < 0.01 mg/kg; 90 % of administered dose excreted within 3 days in rats)

IIA 6.9.1.2 Estimates f of the potential exposure through diet for North America (TMDI)

An estimate of potential intake, direct (food made from chemx treated wheat) and indirect (meat, milk, eggs from animals fed with chemx treated wheat) prepared on the basis of the Canadian diet, demonstrated that potential exposure was no more than 0.12 % of the proposed ADI (0.24 mg/kg bw/day) for adults (Table IIA 6.9.1-2) and ranged from 0.2 - 0.4 % of the proposed ADI (0.24 mg/kg bw/day) for infants and children (Table IIA 6.9.1-3). On the basis of these estimates, it was not considered necessary to prepare estimates of actual exposure.

Table IIA 6.9.1-2 Estimate of the TMDI for chemx in adults (60 kg) based on the "Apparent per capita domestic consumption of food in Canada, (1996)"

Commodity	Intake (g/person/day)	Proposed MRL (mg/kg)	Residue Intake
Wheat (total)	167.62	0.02	0.0033524 mg/day
Meat and fat (total)	244.63	0.02	0.0048926 mg/day
Meat by-products (total)	0.49	0.02	0.0000098 mg/day
Dairy Products	349.54	0.02	0.0069908 mg/day
Eggs	27.97	0.02	0.0005594 mg/day
Total Residue Intake			0.015805 mg/day
PDI			0.0002634 mg/kg bw/day
Total Dietary Exposure (% of ADI)			0.11 %
Total Dietary Exposure (% of ADI with 10% of ADI allocated to water)*			0.12 %

* Total dietary exposures for adults, infants and children, recalculated on the basis that 10 % of the proposed ADI of 0.24 mg/kg bw/day is allocated to water consumption.

Table IIA 6.9.1-3 Estimate of the Potential Dietary Intake (PDI) for chemx in Infants and Children.

1996 USDA continuing survey of food intakes by individuals				
Means all person				
Sex and age (years)	**0 - 1 years**	**1 - 5 years**	**6 - 11 years**	**12 - 19 years**
Body weights (kg)	**8.5**	**14.5**	**26.5**	**52**
	Mean quantities consumed (grams/individual/day)			
Total intake of grain products (g)	46	201	281	413
Proposed MRL (mg/kg)	0.02	0.02	0.02	0.02
Residue Intake (mg/child/day)	0.00092	0.00402	0.00562	0.00826
PDI (mg/kg bw/day)	0.0001082	0.0002772	0.000212	0.0001588
PDI as % ADI	**0.0451**	**0.1155**	**0.0883**	**0.0662**
Total intake of milk and milk products	719	465	450	393
Proposed MRL	0.02	0.02	0.02	0.02
Residue Intake (mg/child/day)	0.01438	0.0093	0.009	0.00786
PDI	0.0016917	0.0006413	0.0003396	0.0001511
PDI as % ADI	**0.7049**	**0.2672**	**0.1415**	**0.063**
Total intake of meat and poultry	27	86	161	252
Proposed MRL	0.02	0.02	0.02	0.02
Residue Intake (mg/child/day)	0.00054	0.00172	0.00322	0.00504
PDI	0.0000635	0.0001186	0.0001215	0.0000969
PDI as % ADI	**0.0265**	**0.0494**	**0.0506**	**0.0404**
Total intake of eggs	5	12	9	24
Proposed MRL	0.02	0.02	0.02	0.02
Residue Intake (mg/child/day)	0.0001	0.00024	0.00018	0.00048
PDI	0.0000117	0.0000165	0.0000067	0.0000092
PDI as % ADI	**0.0049**	**0.0069**	**0.0028**	**0.0038**
Total dietary exposure	**0.78**	**0.44**	**0.28**	**0.17**
Total dietary exposure (10% of ADI allocated to water) *	**0.87**	**0.49**	**0.31**	**0.19**

* Total dietary exposures for adults, infants and children, recalculated on the basis that 10 % of the proposed ADI of 0.24 mg/kg bw/day is allocated to water consumption.

IIA 6.11 Summary and evaluation of residue behaviour

The plant metabolism study (wheat) submitted demonstrated that chemx is metabolised in plants. Metabolites identified were desmethyl chemx (metabolite 1), xxxxxxx (metabolite 2), xxxxxx (metabolite 6), xxyx (metabolite 8), xxx (metabolite 5) and xxxx (metabolite 10) - see attachment. At harvest, some 33 to 45 % of the total residue is in the form of parent chemx.

The proposed method of analysis for chemx residues involves the quantitative conversion of chemx to the ethylsulphone metabolite by means of acid hydrolysis and the conversion of those other metabolites that can be hydrolysed to the ethylsulphone metabolite upon hydrolysis with acid. The sulphone is quantified by means of HPLC analysis with fluorescence detection. The residue is calculated as mg/kg of sulphone, expressed as chemx parent equivalent. Residues unaccounted for by the method are not considered to be of toxicological significance. It is proposed that the for regulatory purposes the limit of quantification (LOQ) for the method be set at 0.02 mg/kg.

The programme of supervised field trials conducted (Belgium, Canada, France, Germany, UK and USA), which involved post-emergence application of chemx to wheat, demonstrated that residues in grain and straw collected at normal harvest were below 0.01 mg/kg and 0.1 mg/kg respectively. Considering these results, the proposed MRL for chemx in wheat grain is 0.02 mg/kg with a minimum pre-harvest interval of 67 days, expressed in terms of the latest growth stage proposed for application - GS 39 (flag leaf ligule just visible).

It is considered unlikely, that residue levels greater than the proposed LOQ of 0.02 mg/kg will occur in succeeding crops following use of chemx as proposed (20 g as/ha). If deemed necessary, further work to determine whether or not residues greater than 0.02 mg/kg could occur in succeeding crops where such crops follow a succession of treated winter wheat crops each of which had been treated with an application of 20 g as/ha per annum of chemx, will be undertaken.

Potential exposure to chemx in the diet is very low. At the proposed application rate of 20 g as/ha, residues of residues above 0.01 mg/kg are expected to occur in animal products such as milk, eggs and meat, are expected to be less than 0.01 mg/kg. On the basis of WHO European region diet, it was estimated that theoretical maximum daily intakes are no more than 0.1% of the proposed ADI (0.24 mg/kg/day), providing a large safety margin for consumers. On the basis of north American dietary patterns, theoretical maximum daily intakes are no more than 0.12 % of the proposed ADI (0.24 mg/kg/day), in the case of adults, and no more 0.9 % of the proposed ADI in the case of infants.

Attachment

CHEMX METABOLITE KEY : NAMES, STRUCTURES & STUDIES WHERE FOUND

[Number] in *Tier II* text refers to ID Number below

ID No	Trivial Name	Chemical Abstracts Name	Structure	Where Found
1	Chemx			Wheat forage, wheat straw
2	Xxxxxxx Metabolite 2			Hydrolysis, aerobic soil, aquatic sediment, wheat forage, wheat straw, rotation crops, rat (urine and faeces)
3	Metabolite 3			Hydrolysis, aerobic soil, aquatic sediment, aqueous photolysis
4	desmethyl chemx Metabolite 1			Aerobic soil, aquatic sediment, wheat forage, wheat straw, rat (urine and faeces)
5	Xxxx Metabolite 10			Aerobic soil, aqueous photolysis
6	Xxxxxx Metabolite 6			Lysimeter leachate, wheat forage, wheat straw
7	Xxx Metabolite 5			Aqueous photolysis, soil photolysis, wheat forage, wheat straw
8	Metabolite 7			Aqueous photolysis, Common chemophore or analyte for residue method

Attachment (Continued)

ID No	Trivial Name	Chemical Abstracts Name	Structure	Where Found
9	Metabolite 10			Aqueous photolysis, wheat forage, wheat straw
10	Xxyx Metabolite 8			Aqueous photolysis, wheat forage, wheat straw
11	Metabolite 9			Aqueous photolysis
12	N-hydroxy Metabolite 5			Aqueous photolysis
13	5-Hydroxy-OEC 1000			Rat (urine and faeces)
14	Rearrangement product			Chemophore (analyte) for analysis of OEC 1000 in water and in soil storage stability
15	Metabolite 11			Rat (urine)